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(57) Abstract

Diaminopyrimidine compounds and their use as inhibitors of gastric acid secretion.

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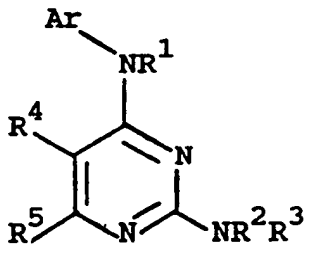
DIAMINOPYRIMIDINE COMPOUNDS

The present invention relates to substituted 2,4-diaminopyrimidine derivatives, processes for their preparation, intermediates useful in their preparation, pharmaceutical compositions containing them and their use in therapy.

Accordingly the present invention provides, in a first aspect compounds of structure (I)



(I)

in which

Ar is a phenyl ring which can be optionally substituted by one to three groups selected from hydroxy, halogen, CF_3, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, cyano, amino, carbamoyl, carboxy or C_{1-4}alkanoyl;

R^1 is hydrogen or C_{1-4}alkyl;

R^2 and R^3 are the same or different and are each hydrogen, C_{1-4}alkyl or Ar^1 where Ar^1 is as defined for Ar; or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated or unsaturated ring optionally containing one or more further heteroatoms.

one of R^4 and R^5 is hydrogen or C_{1-4}alkyl; and the other is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, amino, C_{1-4}alkanoyl, C_{1-4}alkylthioC_{1-4}alkyl, $Ar^2(CH_2)_nOC_{1-4}$alkyl, in which Ar^2 is an optionally substituted phenyl ring as defined for Ar and n is 0 to 4; or $-(CH_2)_mAr^3$, in which m is 1 to 4 and Ar^3 is an optionally substituted phenyl ring as defined for Ar; or R^4 and R^5 together with the carbon atoms to which they are attached form a 5- or 6-membered ring, optionally containing one or more heteroatoms;

and pharmaceutically acceptable salts thereof.

Suitably, Ar is an unsubstituted phenyl ring or a phenyl ring substituted by 1 to 3 substituents selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-4}alkanoyl or trifluoromethyl. More suitably, Ar is an unsubstituted phenyl ring or one substituted by two substituents selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, halogen, cyano, amino, hydroxy, carbamoyl, carboxy, C_{1-4}alkanoyl or trifluoromethyl. More preferably, Ar is an unsubstituted phenyl ring or one substituted by two substituents selected from C_{1-4}alkyl and C_{1-4}alkoxy. Most preferably, Ar is an unsubstituted phenyl ring or one substituted by a single substituent selected from the above-noted groups, in particular hydroxy, halogen, C_{1-4}alkyl or C_{1-4}alkoxy.

Suitably R^1 is hydrogen or C_{1-4}alkyl; preferably R^1 is C_{1-4}alkyl. Most preferably R^1 is methyl.

Suitably R^2 and R^3 are the same or different and are each hydrogen, C_{1-4}alkyl or a ring Ar^1 or R^2 and

R^3 together with the nitrogen atom to which they are attached form a saturated or unsaturated ring optionally containing one or more further heteroatoms. More suitably one of R^2 and R^3 is hydrogen or C_{1-4}alkyl and the other is hydrogen, C_{1-4}alkyl or a ring Ar^1 or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated or unsaturated ring optionally containing one or more further heteroatoms. Most suitably, one of R^2 and R^3 is hydrogen or C_{1-4}alkyl and the other is hydrogen, C_{1-4}alkyl or any Ar^1. Preferably one of R^2 and R^3 is hydrogen or C_{1-4}alkyl and the other is a ring Ar^1; more preferably one of R^2 and R^3 is hydrogen and the other is a ring Ar^1.

Suitably Ar^1 is an unsubstituted phenyl ring or a phenyl ring substituted as defined for Ar. Preferably Ar^1 is an unsubstituted phenyl ring or a phenyl ring substituted by 1 or 2 substituents selected from C_{1-4}alkyl and halogen.

Suitably, one of R^4 and R^5 is hydrogen or C_{1-4}alkyl, and the other is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, amino, C_{1-4}alkanoyl, C_{1-4}alkylthio-C_{1-4}alkyl, $Ar^2(CH_2)_nOC_{1-4}$alkyl, in which Ar^2 is an optionally substituted phenyl ring as described for Ar and n is 0 to 4, or $-(CH_2)_mAr^3$ in which Ar^3 is an optionally substituted phenyl ring as described for Ar and m is 1 to 4; or R^4 and R^5 together with the carbon atoms to which they are attached form a 5- or 6-membered ring optionally containing one or more heteroatoms. Preferably R^4 is hydrogen or C_{1-4}alkyl and R^5 is C_{1-4}alkyl, hydroxyC_{1-4}alkyl or C_{1-4}alkoxyalkyl; or R^4 and R^5 together with the carbon atoms to which they are attached form a 6-membered carbocyclic ring.

Suitably Ar^2 is an optionally substituted phenyl ring as described for Ar; preferably Ar^2 is an unsubstituted phenyl ring. Suitably n is 0 to 4, preferably n is 1.

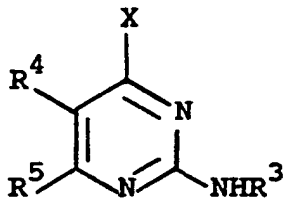
Suitably Ar^3 is an optionally substituted phenyl ring as described for Ar; preferably Ar^3 is an unsubstituted phenyl ring. Suitably m is 1 to 4, preferably m is 1.

Suitable rings formed by R^4 and R^5 together with the carbon atoms to which they are attached, containing one or more heteroatoms include, for example, 5- or 6-membered rings containing a sulphur, oxygen or nitrogen atom and, in addition, 5- or 6-membered rings containing a sulphur atom in which the sulphur atom is in the form of the sulphoxide or sulphone, as hereinafter described in the examples.

C_{1-4}alkyl groups (either alone or as part of another group) can be straight or branched.

It will be appreciated that compounds of structure (I) in which one or more of R^1 to R^5 is a C_{3-4}alkyl group (either alone or as part of another group) may contain an assymetric centre due to the presence of the C_{3-4}alkyl group. Such compounds will exist as two (or more) optical isomers (enantiomers). Both the pure enantiomers, racemic mixtures (50% of each enantiomer) and unequal mixtures of the two are included within the scope of the present invention. Further, all diastereomeric forms possible (pure enantiomers and mixtures thereof) are within the scope of the invention.

The compounds of the present invention can be prepared by processes analogous to those known in the art. The present invention therefore provides in a further aspect a process for the preparation of a compound of structure (I) or a pharmaceutically acceptable salt thereof which comprises reaction of a compound of structure (II)



(II)

in which R^3 to R^5 are as described for structure (I), and X is a group displaceable by an amine, with an amine of structure $ArNR^1H$ in which Ar and R^1 are as described for structure (I), and optionally thereafter, forming a pharmaceutically acceptable salt.

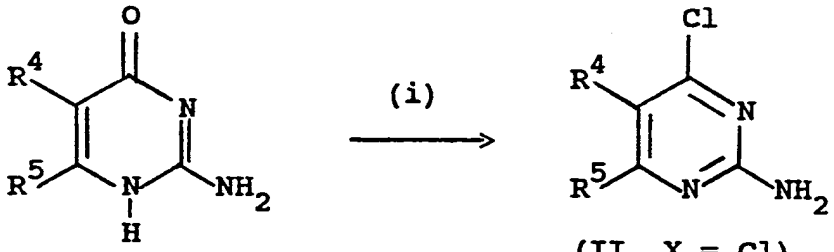
Suitable groups displaceable by an amine X will be apparent to those skilled in the art and include, for example, halogen in particular chlorine, SC_{1-4}alkyl such as methylthio and phenoxy.

Reaction of a compound of structure (II) with an amine ArR^1NH is suitably carried out in an inert solvent at elevated temperature. Preferably the reaction is carried out in the absence of a solvent in a sealed receptacle at elevated temperature. Most preferably in an inert solvent for example dioxan, at reflux temperature.

Pharmaceutically acceptable acid addition salts of the compounds of structure (I) can be prepared by standard procedures by, for example, reaction with suitable organic and inorganic acids the nature of which will be apparent to persons skilled in the art. For example, pharmaceutically acceptable salts can be formed by reaction with hydrochloric, sulphuric, or phosphoric acids; aliphatic, aromatic or heterocyclic sulphonic acids or carboxylic acids such as, for example, citric, maleic or fumaric acids, or methyl sulphonic acid.

The intermediate compounds of structure (II) can be prepared by procedures analogous to those known in the art. The amines of structure ArR^1NH are available commercially or can be prepared by standard techniques well known to those skilled in the art of organic chemistry.

For example, compounds of structure (II) in which R^2 and R^3 are hydrogen can be prepared by the following procedure :

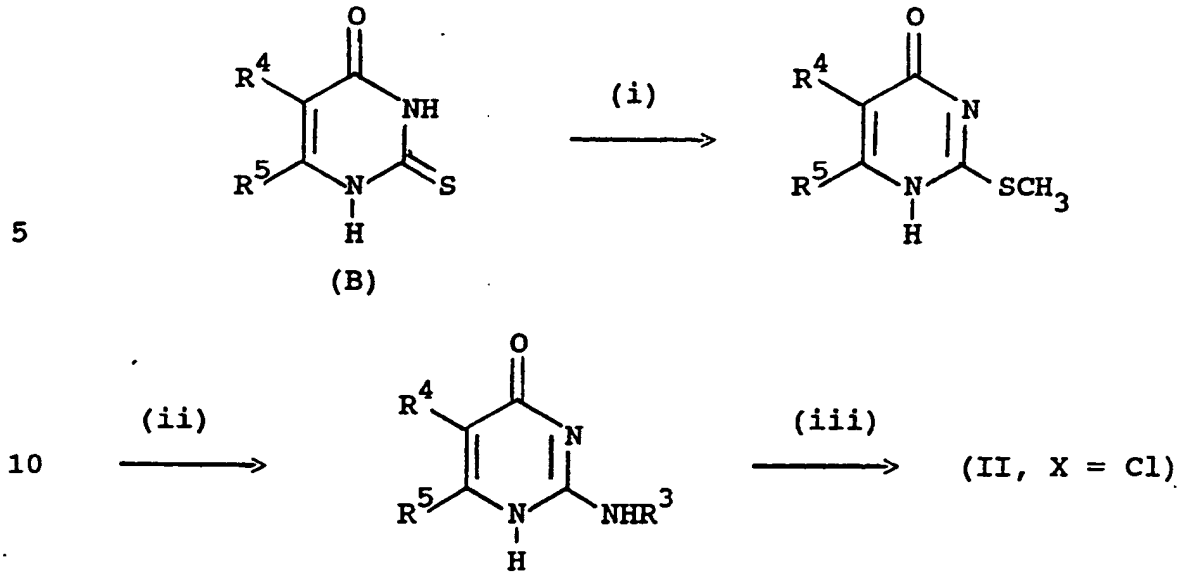


(A) (II, X = Cl)

(i) $POCl_3$.

The starting materials (A) are known or can be prepared by standard procedures.

Compounds of structure (II) in which R^3 is other than hydrogen can be prepared by the following procedures :



(B)

(i) CH_3I;

(ii) R^3NH_2

(iii) $POCl_3$

Compounds (B) are known or can be prepared by standard techniques.

The compounds of structure (I) and their pharmaceutically acceptable salts exert an anti-secretory effect by inhibition of the gastrointestinal H^+K^+ATPase enzyme.

In a further aspect therefore the present invention provides compounds of structure (I) and pharmaceutically acceptable salts thereof for use in therapy.

The compounds of structure (I) and their pharmaceutically acceptable salts inhibit exogenously and endogenously stimulated gastric acid secretion and are

useful in the treatment of gastrointestinal diseases in mammals, in particular humans. Such diseases include, for example, gastric and duodenal ulcers, and Zollinger-Ellison Syndrome. Further, the compounds of structure (I) can be used in the treatment of other disorders where an anti-secretory effect is desirable for example in patients with gastritis, NSAID induced gastritis, gastric ulcers, acute upper intestinal bleeding, in patients with a history of chronic and excessive alcohol consumption, and in patients with gastro oesophageal reflux disease (GERD).

In therapeutic use, the compounds of the present invention are usually administered in a standard pharmaceutical composition.

The present invention therefore provides in a further aspect pharmaceutical compositions comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The compounds of structure (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as liquids, for example syrups, suspensions or emulsions, tablets, capsules and lozenges.

A liquid formulation will generally consist of a suspension or solution of the compound or pharmaceutically acceptable salt in a suitable liquid carrier(s) for example, ethanol, glycerine, non-aqueous solvent, for example polyethylene glycol, oils, or water with a suspending agent, preservative, flavouring or colouring agent.

A composition in the form of a tablet can be prepared using any suitable pharmaceutical carrier(s) routinely used for preparing solid formulations. Examples of such carriers include magnesium stearate, starch, lactose, sucrose and cellulose.

A composition in the form of a capsule can be prepared using routine encapsulation procedures. For example, pellets containing the active ingredient can be prepared using standard carriers and then filled into a hard gelatin capsule; alternatively, a dispersion or suspension can be prepared using any suitable pharmaceutical carrier(s), for example aqueous gums, celluloses, silicates or oils and the dispersion or suspension then filled into a soft gelatin capsule.

Typical parenteral compositions consist of a solution or suspension of the compound or pharmaceutically acceptable salt in a sterile aqueous carrier or parenterally acceptable oil, for example polyethylene glycol, polyvinyl pyrrolidone, lecithin, arachis oil or sesame oil. Alternatively, the solution can be lyophilised and then reconstituted with a suitable solvent just prior to administration.

A typical suppository formulation comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent such as polymeric glycols, gelatins or cocoa butter or other low melting vegetable or synthetic waxes or fats.

Preferably the composition is in unit dose form such as a tablet or capsule.

Each dosage unit for oral administration contains preferably from 1 to 250 mg (and for parenteral administration contains preferably from 0.1 to 25 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The pharmaceutically acceptable compounds of the invention will normally be administered in a daily dosage regimen (for an adult patient) of, for example, an oral dose of between 1 mg and 500 mg, preferably between 1 mg and 250 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 100 mg, preferably between 0.1 mg and 25 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy, for example for a week or more.

In addition, the compounds of the present invention can be co-administered with further active ingredients in particular when used to treat conditions caused or exacerbated by gastric acidity. Such ingredients include antacids (for example magnesium carbonate or hydroxide and aluminium hydroxide), non-steroidal anti-flammatory drugs (for example indomethacin, aspirin or naproxen), steroids, or nitrite scavengers (for example ascorbic acid or aminosulphonic acid), or other drugs used for treating gastric ulcers (for example pirenzipine, prostanoids for example 16,16 dimethyl PGE_2, or histamine H_2-antagonists (for example, cimetidine).

The present invention also provides in a still further aspect, a method of treatment of gastrointestinal diseases caused or exacerbated by gastric acid in mammals,

including man which comprises administering to a subject in need thereof an effective amount of a compound of structure (I) or a pharmaceutically acceptable salt thereof.

The following examples illustrate the invention. Temperatures are recorded in degrees centigrade.

Example 1

2-Amino-4-methyl-6-[(2-methylphenyl)amino]pyrimidine hydrochloride

2-Amino-4-chloro-6-methylpyrimidine (2.0 g, 0.014 m) and o-toluidine (4.0 g - excess) were mixed at room temperature and heated with stirring under nitrogen in an oil-bath. The oil-bath temperature was raised to 165°, held thus for two hours and the reactants then cooled to room temperature. Acetone was added to the resulting oil and on scratching a crystalline solid separated. After standing at ~0° overnight the solid was collected washed with acetone and dried (3.47 g, pale-pink solid). This solid was re-crystallised from absolute ethanol/diethyl ether to give the title compound as its hydrochloride salt (2.64 g), m.p. = 229-231°.

$C_{12}H_{14}N_4 \cdot HCl$.

Found: C 57.7, H 6.1, N 22.3, Cl^- 14.0

Requires: C 57.5, H 6.0, N 22.4, Cl^- 14.1

Example 2

2-Amino-4,5-dimethyl-6-[(2-methylphenyl)amino]pyrimidine hydrochloride

Substituting 2-amino-4-chloro-5,6-dimethyl-pyrimidine (2.1 g, 0.0133 m) for 2-amino-4-chloro-6-methylpyrimidine and using corresponding molar proportions of the other reagents in Example 1 produced a solid (3.16 g). This solid was re-crystallised from isopropanol to give the

title compound (2.63 g) as its hydrochloride salt, m.p. = 305-306°

$C_{13}H_{16}N_4 \cdot HCl$.

Found: C 58.8, H 6.4, N 21.1, Cl^- 13.2

Requires: C 59.0, H 6.5, N 21.2, Cl^- 13.4

Example 3

2-Amino-4-[(2-methylphenyl)amino]pyrimidine

2-Amino-4-chloropyrimidine (2.2 g, 0.01698 m) and o-toluidine (4.0 g, excess) were mixed at room temperature and heated with stirring (under an air condenser) in an oil-bath at 165-170° for two hours. After cooling the violet oil was taken up in a small volume of water and 2N HCl added dropwise with stirring to give a suspension at pH 4.5. This was extracted with chloroform (4 x 200 ml) to remove o-toluidine. The aqueous solution remaining was basified with NaOH (→ pH 8.5) and again extracted with chloroform (4 x 200 ml). The latter chloroform extracts were combined, dried (K_2CO_3) and evaporated to dryness to give a glass which crystallised on standing. This material was re-crystallised from ethanol/water to give the title compound (1.64 g) as a very pale-pink solid, m.p. = 118-120°.

$C_{11}H_{12}N_4$

Found: C 65.8, H 6.0, N 27.9

Requires: C 66.0, H 6.0, N 28.0

Example 4

2-Amino-4-methyl-6-(N-methylphenylamino)pyrimidine hydrochloride

Substituting N-methylaniline (4.0 g - excess) for

o-toluidine and using corresponding molar proportions of the other reagents in Example 1 gave a white solid (2.0 g). This was re-crystallised from ethanol/ether to give the title compound (1.21 g) as its hydrochloride salt, m.p. = 243-245°.

$C_{12}H_{14}N_4 \cdot HCl$.

Found: C 57.4, H 5.9, N 22.6

Requires: C 57.5, H 6.0, N 22.4

Example 5

2,4-Bis-[(2-methylphenyl)amino]-6-methylpyrimidine hydrochloride

2,4-Dichloro-6-methylpyrimidine (1.63 g, 0.01 m) and o-toluidine (4.28 g, 0.04 m) were mixed at room temperature and heated with stirring in an oil-bath at ~150° for two hours. The cooled reaction mixture was treated with acetone to give a white solid in a pinky-red solution. The solid was collected, washed with acetone and dried to give the title compound (2.65 g) as its hydrochloride salt, m.p. = 216-218°.

$C_{19}H_{20}N_4 \cdot HCl$.

Found: C 67.2, H 6.2, N 16.6, Cl^- 10.0

Requires: C 67.0, H 6.2, N 16.4, Cl^- 10.4

Example 6

2,4-Bis-(N-methylphenylamino)-6-methylpyrimidine

2,4-Dichloro-6-methylpyrimidine (1.63 g, 0.01 m) and N-methylaniline (2.14 g, 0.02 m) were mixed at room temperature and heated with stirring in an oil-bath at

~150° for two hours. The resulting pale-yellow oil was dissolved in water and the aqueous solution basified with saturated aqueous Na_2CO_3 solution. The mixture was extracted with ether and the ethereal solution washed with water and brine, dried and evaporated to dryness to give an oil. This oil was chromatographed on silica gel using methylene chloride as eluting solvent. Fractions were monitored by t.l.c. and appropriate fractions combined and evaporated to give a white solid which was triturated with 40-60 petroleum ether, filtered and dried to give the title compound (0.63 g), m.p. = 63-65°.

$C_{19}H_{20}N_4$

Found: C 75.0, H 6.7, N 18.2

Requires: C 75.0, H 6.6, N 18.4

Example 7

2-(N-Methylphenylamino)-4-[(2-methylphenyl)amino]-6-methylpyrimidine hydrochloride

(i) 4-Chloro-6-methyl-2-(N-methylphenylamino)pyrimidine

6-Methyl-2-(N-methylphenylamino)pyrimidin-4-one (J. Het. Chem. (1984), 21, 1161) (4.6 g, 0.0214 m) and phosphorous oxychloride (20 ml) were mixed at room temperature and heated together at reflux temperature for two hours. The dark-brown solution was cooled and poured onto ice to produce, after decomposition of excess reagent, a yellow acidic solution. This was basified (→ pH 8) with 6N. NaOH and the aqueous mixture extracted with ethyl acetate. The brown organic solution was washed with water, dried and evaporated to give the title compound as a brown oil, 3.06 gms (Mass spectrum M-H = 232).

(ii) 2-(N-methylphenylamino)-4-[(2-methylphenylamino]-6-methylpyrimidine hydrochloride.

4-Chloro-6-methyl-2-(N-methylphenylamino) pyrimidine (3.0 g, oil, 0.0129 m) and o-toluidine (1.38 g, 0.0129 m) were mixed at room temperature and heated in an oil-bath, with stirring, to 140°. After twenty minutes at this temperature the mixture completely solidified. After cooling acetone was added and the solid collected, ground to a powder, washed with more acetone and dried (3.85 g). This solid was re-crystallised from ethanol/ether to give the title compound (2.48 g) as its hydrochloride salt, light-buff, m.p. = 238-240°.

$C_{19}H_{20}N_4 \cdot HCl$.

Found: C 66.9, H 5.9, N 16.4, Cl^- 10.2

Requires: C 67.0, H 6.2, N 16.4, Cl^- 10.4

Example 8

2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-methylpyrimidine hydrochloride

(i) 4-Chloro-6-methyl-2-[(2-methylphenyl)amino]pyrimidine

Substituting 6-methyl-2-[(2-methylphenyl)amino]-pyrimidin-4-one (J.C.S. (1946), 351) (3.63 g, 0.0159 m) for 6-methyl-2-(N- methylphenylamino)pyrimidin-4-one and using corresponding molar proportions of the other reagents in Example 7(i) gave the title compound as an oil (3.94 g), which crystallised on standing under vacuum overnight.

(ii) 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-methylpyrimidine hydrochloride.

4-Chloro-6-methyl-2-[(2-methylphenyl)amino]pyrimidine (3.9 g, 0.01674 m) and N-methylaniline (1.79 g, 0.01674 m) were mixed at room temperature and heated with stirring in an oil-bath at 140° for three hours. The red-oil produced was cooled to ~50° and acetone added to give, on scratching a light buff solid which was collected, washed with acetone and dried (3.56 g). This solid was re-crystallised from ethanol/ether to give the title compound (3.01 g) as light-buff needles, m.p. = 203-205° (hydrochloride salt).

$C_{19}H_{20}N_4 \cdot HCl$.

Found: C 66.9, H 6.3, N 16.5, Cl^- 10.3

Requires: C 67.0, H 6.2, N 16.4, Cl^- 10.4

Example 9

2-[(2-Methylphenyl)amino]-4-(phenylamino)-6-methyl-pyrimidine hydrochloride

Substituting aniline (0.718 g, 0.00644 m) for N-methylaniline and using corresponding molar proportions of the other reagents in Example 8(ii), gave a buff-coloured solid (1.33 g). This was re-crystallised from ethanol/diethyl ether to give the title compound (1.04 g) as its hydrochloride salt (pale-buff), m.p. = 212-214°.

$C_{18}H_{18}N_4 \cdot HCl$.

Found: C 65.9, H 5.9, N 17.0

Requires: C 66.2, H 5.9, N 17.1

Example 10

2-[(2-Methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)-6-methylpyrimidine hydrochloride

Substituting N-methyl-o-toluidine (0.935 g, 0.00772 m)

for N-methylaniline and using corresponding molar proportions of the other reagents in Example 8(ii), gave after addition of acetone, a red solution (no solid crystallised at this stage). Diethyl ether was added to this solution and after standing overnight in the fridge a solid separated and was collected, washed with acetone/ diethyl ether and dried to give a light-grey powder (0.7 g). This was crystallised from acetone/diethyl ether to give the title compound (0.35 g) as its hydrochloride salt, m.p. = 179-180°.

$C_{20}H_{22}N_4 \cdot HCl$.

Found: C 67.3, H 6.5, N 15.2

Requires: C 67.7, H 6.5, N 15.8

Example 11

2-Amino-4-[(2-methylphenyl)amino]-6-n-propyl pyrimidine.

(i) 2-Amino-4-chloro-6-n-propylpyrimidine

2-Amino-6-n-propylpyrimidin-4-one (J.C.S.(C), (1968), 2358-67) (6.7 g, 0.0437 m) and phosphorus oxychloride (40 ml) were mixed at room temperature and heated at reflux temperature for three hours to produce an orange solution. This was cooled, poured onto ice and stirred for several hours. The aqueous medium was neutralised with 6N. NaOH and again stirred in ice. A brown solid precipitate resulted which was extracted into ethyl acetate. The organic extracts were combined, washed, dried and evaporated to give a buff solid which was immediately used in the next stage of the synthesis (Mass spectrum → M/e = 171).

(ii) 2-Amino-4-[(2-methylphenyl)amino]-6-n-propyl pyrimidine

2-Amino-4-chloro-6-n-propylpyrimidine (1.65, 0.00965 m) and o-toluidine (4.0 g - excess) were mixed at room temperature and heated with stirring in an oil-bath at 140° for four hours. After cooling acetone was added to give a purply-red solution. Diethylether was added to precipitate a purple oil. The solution was decanted off and the residual oil triturated several times with diethylether. The oil was dissolved in acetone, water added and the purple solution basified with aqueous Na_2CO_3 when a solid precipitated which was collected, washed with water and dried (2.25 g). This material was crystallised from acetone/water to give the title compound (1.55) as buff needles, m.p. = 151-153°.

$C_{14}H_{18}N_4$

Found: C 69.4, H 7.5, N 23.3

Requires: C 69.4, H 7.5, N 23.1

Example 12

2-Amino-4-(2-methyl-4-hydroxyphenylamino)-6-n-propyl-pyrimidine

Substituting 4-amino-m-cresol (4.0 gms, XS) for o-toluidine and using corresponding molar proportions of the other reagents in Example 11(ii) gave a dark-red solution after addition of acetone to the reaction mixture. Water was added followed by aqueous Na_2CO_3 to basify the solution and precipitate a black solid which was filtered off and discarded. The aqueous filtrate was extracted with ethyl acetate and the combined organic extracts back-washed with water. The ethyl acetate was

dried and evaporated to yield a dark-brown glass which solidified on treatment with diethyl ether and was collected, washed with ether and dried to a buff powder (2.72 g). This was charcoated in ethanol, concentrated and stood at 0° to give the title compound (1.14 g) as a buff-coloured crystalline solid, m.p. = 199-200°.

$C_{14}H_{18}N_4O$

Found: C 64.8, H 6.9, N 21.7

Requires: C 65.1, H 7.0, N 21.7

Example 13

2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-n-propylpyrimidine hydrochloride

(i) 2-[(2-Methylphenyl)amino]-6-propylpyrimidin-4-one

2-Methylthio-6-propylpyrimidin-4-one (Eur.J.Med. Chem., (1988), 23, 53) (9.21 g, 0.05 m) and o-toluidine (5.5 g, 0.052 m) were mixed at room temperature and heated with stirring in an oil-bath at 170° for five hours. Effluent gases were passed through a CHLOROS trap. The reaction mixture was cooled to produce a solid. Cold methanol was added and the insoluble solid collected, washed with cold methanol and dried to a light-grey solid (6.14 g) which was used immediately.

(ii) 4-Chloro-6-n-propyl-2-[(2-methylphenyl)amino]-pyrimidine

The product from Example 13 i) above (5.5 g, 0.0226 m) and phosphorous oxychloride (30 ml) were mixed at room temperature and heated at reflux temperature for

2½ hours. The cooled solution was poured onto ice and the aqueous mixture neutralised with 6N. NaOH. The mixture was extracted with ethyl acetate, the organic extracts washed with water, dried and evaporated to give a brown oil which crystallised on scratching (5.5 g) and was used immediately.

(iii) 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-6-n-propylpyrimidine hydrochloride.

The product from Example 13 ii) above (2.62 g, 0.01 m) and N-methylaniline (1.07 g, 0.01 m) were mixed at room temperature and heated, with stirring, in an oil-bath at 140° for two hours. The mixture, initially an oil, had virtually solidified by this time and was cooled, acetone added and the insoluble solid collected (2.12 g). This was crystallised from ethanol/diethyl ether to give the title compound (1.53 g) as its blue-white hydrochloride salt, m.p. = 170-172°.

$C_{21}H_{24}N_4 \cdot HCl$.

Found: C 68.2, H 6.8, N 15.1, Cl^- 9.6

Theory: C 68.4, H 6.8, N 15.2, Cl^- 9.6

Example 14

2-[(4-Fluoro-2-methylphenyl)amino]-4-(N-methylphenylamino)-6-n-propylpyrimidine hydrochloride

(i) 2-[(4-Fluoro-2-methylphenyl)amino]-6-n-propyl pyrimidin-4-one.

Substituting 4-fluoro-2-methylaniline (4.0 g, 0.032 M) for o-toluidine and using corresponding molar

proportions of the other reagents in Example 13(i) gave a crystalline solid which was collected, washed with cold methanol and dried, to give a grey solid (5.36 g).

(ii) 4-Chloro-6-n-propyl-2-[(4-fluoro-2-methylphenyl)-amino]pyrimidine.

Substituting the product of Example 14(i) above (5.2 g, 0.0199 m) for 2-[(2-methylphenyl)amino]-6-n-propylpyrimidin-4-one and using corresponding molar proportions of the other reagents in Example 13(ii) gave a brown oil which crystallised on standing (3.4 gms) which was used immediately.

(iii) 2-[(4-Fluoro-2-methylphenyl)amino]-4-(N-methyl-phenylamino)-6-n-propylpyrimidine hydrochloride

4-Chloro-6-n-propyl-2-[(4-fluoro-2-methylphenyl)-amino]pyrimidine (3.0 g, 0.0107 m) and N-methylaniline (2.0 g, XS) were mixed at room temperature and heated, with stirring, in an oil-bath at 146° for 2¼ hours. The brown oil produced was cooled, acetone added and, on standing at 0° overnight, crystals separated which were collected, washed with acetone and dried (1.56 g). This solid was re-crystallised from ethanol/diethyl ether to give the title compound (0.92 g) as its colourless hydrochloride salt, m.p. = 165-167°.

$C_{21}H_{23}FN_4 . HCl.$

Found: C 65.1, H 6.3, N 14.5, Cl^- 9.1

Requires: C 65.2, H 6.3, N 14.5, Cl^- 9.2

Example 15

2-[(4-Fluoro-2-methylphenyl)amino]-4-(N-methyl-2-methyl-phenylamino)-6-n-propylpyrimidine hydrochloride

Substituting N-methyl-o-toluidine (0.664 g, 0.00549 m) for N-methylaniline and using corresponding molar proportions of the other reagents in Example 14(iii) gave a red acetone solution after the heated reaction mixture had been allowed to cool. (N.B. In this example some white crystalline solid sublimed out of the heated reaction vessel during the reaction - this was shown by t.l.c. to be starting amine hydrochloride). The red acetone solution was evaporated to dryness and the residual oil dissolved in ethyl acetate. The red ethyl acetate solution was washed with aqueous Na_2CO_3, H_2O, 2N.HCl and water, dried and evaporated to a buff solid (0.63 g). This was crystallised from ethanol/ diethylether to give the title compound (0.42 g) as its pale-buff hydrochloride salt, m.p. = 170-172°.

$C_{22}H_{25}FN_4 . HCl$.

Found: C 65.5, H 6.4, N 13.8

Requires: C 65.9, H 6.5, N 14.0

Example 16

2-Amino-4-benzyl-6-[(2-methylphenyl)amino]pyrimidine

(i) 2-Amino-4-benzyl-6-chloropyrimidine.

2-Amino-6-benzylpyrimidin-4-one (J.Pharm.Sci. (1964), 53, 1317) (6.2 g, 0.0308 m) and phosphoryl chloride (40 ml)

were mixed at room temperature and heated under reflux for three hours. The mixture was cooled, poured onto ice and the aqueous mixture basified with 2N.NaOH and extracted with chloroform. The chloroform extracts were combined, washed with water and brine, dried and evaporated to a green oily solid (2.25 g) which was used immediately.

(ii) 2-Amino-4-benzyl-6-[(2-methylphenyl)amino]pyrimidine

The product from Example 16(i) above (2.2 g, 0.01023 m) and o-toluidine (4.0 g, XS) were mixed at room temperature and heated with stirring in an oil-bath at 150° for three hours. The mixture was cooled, dissolved in methanol and acidified with 2N.HCl. The whole mixture was evaporated to dryness and the residue dissolved in distilled water (a little insoluble material was filtered off and discarded). The clear aqueous solution was basified with 2N NaOH to precipitate a light-buff solid (1.2 g). This was crystallised, first from acetone and finally from methanol/acetone to give the title compound (0.5 g), m.p. = 197-199°.

$C_{18}H_{18}N_4$

Found: C 74.5, H 6.1, N 19.3

Requires: C 74.5, H 6.3, N 19.3

Example 17

6-Benzyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino)-pyrimidine hydrochloride

(i) 6-Benzyl-2-[(2-methylphenyl)amino]pyrimidin-4-one

6-Benzyl-2-methylthiopyrimidin-4-one (Eur.J.Med.Chem. (1988), 23, 53) (8.37 g, 0.03608 m) and o-toluidine

(4.06 g, 0.038 m) were mixed at room temperature and heated with stirring in an oil-bath at 170° for six hours, effluent gases being passed through a CHLOROS trap. The mixture was then cooled and treated at room temperature overnight with a mixture of methanol/acetone, 1:1. A yellow solid was produced which was collected, washed with acetone and dried (6.1 g). A portion was re-crystallised from methanol to give the title compound as an off-white solid, m.p. = 153-155°.

$C_{18}H_{17}N_3O$

Found: C 74.4, H 5.8, N 14.3

Requires: C 74.2, H 5.9, N 14.4

(ii) 4-Benzyl-6-chloro-2-[(2-methylphenyl)amino]pyrimidine

The product of Example 17(i) above (5.3 g, 0.0182 m) and phosphoryl chloride (30 ml) were mixed at room temperature and heated under reflux for 2½ hours. The orange solution was then cooled, poured onto ice and the aqueous mixture neutralised with 40% NaOH. The mixture was extracted with ethyl acetate and the combined organic extracts washed, dried and evaporated to a yellow oil (5.1 g) which was used immediately without further purification.

(iii) 6-Benzyl-2-[(2-methylphenyl)amino]-4-(N-methyl-phenylamino)pyrimidine hydrochloride

The product from Example 17(ii) above (5.1 g, 0.0165 m) and N-methylaniline (3.53 g, 0.033 m) were mixed at room temperature and heated with stirring in an oil-bath at 150° for 2½ hours. The mixture was cooled and acetone added at ~70°. The mixture was boiled to give a clear

solution and cooled when a solid crystallised which was collected, washed with acetone and dried. The material was re-crystallised twice from ethanol/diethyl ether to give the title compound (2.18 g) as its blue-white hydrochloride salt, m.p. = 183-185°.

$C_{25}H_{24}N_4 . HCl.$

Found: C 71.8, H 6.1, N 13.3, Cl^- 8.3

Requires: C 72.0, H 6.0, N 13.4, Cl^- 8.5

Example 18

5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(phenylamino)-pyrimidine hydrochloride

(i) 5,6-Dimethyl-2-[(2-methylphenyl)amino]pyrimidin-4-one

5,6-Dimethyl-2-methylthiopyrimidin-4-one (Eur.J.Med. Chem. (1988), 23, 53) (24.0 g, 0.14 m) and o-toluidine (30 ml) were stirred together under nitrogen at 200-220° for 12 hours with effluent gases being passed through a CHLOROS trap. After cooling the reaction mixture was triturated with pentane, the insoluble solid filtered off and crystallised from methanol/ethyl acetate to give the title compound (23.1 g), m.p. = 194-5°.

(ii) 4-Chloro-5,6-dimethyl-2-[(2-methylphenyl)amino pyrimidine

The product of Example 18(i) above (13.0 g, 0.057 m) and phosphorous oxychloride (200 ml) were heated together at reflux temperature for two hours. The $POCl_3$ was distilled off and ice added carefully to the residue which was then basified with sodium hydroxide. The aqueous

mixture was extracted with chloroform and the combined organic extracts dried and evaporated to dryness. The residue was chromatographed on silica gel in chloroform and appropriate fractions combined, evaporated and the residue triturated with pentane to yield the title compound as a solid (8.5 g), m.p. = 95-98°.

(iii) 5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(phenylamino)pyrimidine hydrochloride

The product of Example 18(ii) above (2.5 g, 0.01 m) and aniline (0.93 g, 0.01 m) were heated at reflux temperature in dry tetrahydrofuran (30 ml) for nine hours. The solid which crystallised out on cooling was filtered off and re-crystallised from methanol/isopropanol/diethyl ether to yield the title compound (2.7 g) as its hydrochloride salt, m.p. = 257-259°.

$C_{19}H_{20}N_4 \cdot HCl$.

Found: C 67.0, H 6.2, N 16.4, Cl^- 10.4

Requires: C 67.1, H 6.1, N 16.4, Cl^- 10.4

Example 19

5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl amino)pyrimidine hydrochloride

A mixture of 4-chloro-5,6-dimethyl-2-[(2-methylphenyl)amino] pyrimidine (1.17 g, 0.005 m) and N-methyl-o-toluidine (6.0 ml) were heated together at 140° for six hours. After cooling ether was added to remove excess N-methyl-o-toluidine. Decanting off the ether and crystallisation of the solid residue from isopropanol/ether gave the title compound (0.7 g) as its hydrochloride salt, m.p. = 192-194°.

$C_{21}H_{24}N_4 \cdot HCl$.

Found: C 68.1, H 6.8, N 15.0

Requires: C 68.4, H 6.8, N 15.2

Example 20

5,6-Dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-phenylamino)pyrimidine hydrochloride

A mixture of 4-chloro-5,6-dimethyl-2-[(2-methyl-phenyl)amino]pyrimidine (2.5 g, 0.01 m) and N-methylaniline (1.07 g, 0.01 m) in dry tetrahydrofuran (30 ml) was heated at reflux temperature for six hours. After cooling, ether was added to precipitate a solid which was collected, washed with ether and crystallised from isopropanol/ether to yield the title compound (1.61 g) as its hydrochloride salt, m.p. = 199-200°.

$C_{20}H_{22}N_4 \cdot HCl$.

Found: C 67.8, H 6.6, N 15.3, Cl^- 9.8

Requires: C 67.8, H 6.5, N 15.8, Cl^- 10.0

Example 21

5-Methyl-6-n-propyl-2-[(2-methyl)phenyl)amino]-4-(N-methyl-2-methyl phenylamino)pyrimidine hydrochloride

(i) 2-[(2-Methylphenyl)amino]-5-methyl-6-n-propyl-pyrimidin-4-one

2-Methylthio-5-methyl-6-n-propylpyrimidin-4-one (C.A. 84, P164836n) (16.0 g, 0.08 m) and o-toluidine (30 ml) were heated together at 200° (oil-bath temp) for six hours.

After cooling, the mixture was triturated with pentane and the pentane decanted. The residual solid was crystallised from methanol/isopropylacetate to yield the title compound (10.5 g), m.p. = 192-194°.

(ii) 4-Chloro-5-methyl-6-n-propyl-2-[(2-methylphenyl)-amino]pyrimidine

The product of Example 21(i) above and phosphorous oxychloride (50 ml) were heated together under reflux for two hours. The $POCl_3$ was distilled off and ice carefully added to the residue. The aqueous mixture was basified with sodium hydroxide and extracted with chloroform. The combined chloroform extracts were concentrated to a low volome and chromatographed on silica gel with chloroform as eluent. Appropriate fractions were combined and evaporated to an oil (11.0 g) which was used immediately below.

(iii) 5-Methyl-6-n-propyl-2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)pyrimidine hydrochloride

The product of Example 21(ii) above (5.5 g, 0.02 m) and N-methyl-o-toluidine (2.4 g, 0.02 m) in tetrahydrofuran (45 ml) were heated together at reflux temperature for three hours, cooled and concentrated to a low volume. Ether was added and the precipitated solid collected, washed with ether and re-crystallised twice from isopropylacetate to give the title compound (1.05 g) as its hydrochloride salt, m.p. = 170-171°.

$C_{23}H_{28}N_4 . HCl.$

Found: C 69.6, H 7.4, N 13.9, Cl^- 8.8

Requires: C 69.6, H 7.4, N 14.1, Cl^- 8.9

Example 22

5-Methyl-6-n-propyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino) pyrimidine hydrochloride

Substituting N-methylaniline (2.14 g, 0.02 m) and using corresponding molar proportions of the other reagents in Example 21(iii) gave a crystalline solid directly from the tetrahydrofuran reaction mixture. This was collected and washed with ether to give the title compound (4.5 g) as its hydrochloride salt, m.p. 178-179°.

$C_{22}H_{26}N_4 \cdot HCl$.

Found: C 69.3, H 7.3, N 14.6, Cl^- 9.2

Requires: C 69.0, H 7.1, N 14.6, Cl^- 9.3

Example 23

2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride !SK&F 99119!

(i) 2-Thioxo-5,6,7,8-tetrahydroquinazolin-4-one.

Sodium (8.5 g, 0.37 mol) was dissolved in absolute ethanol (300 mL) and treated with ethyl-2-oxocyclohexanecarboxylate (40 g, 0.186 mol) and thiourea (14.2 g, 0.186 mol) and refluxed for 4 hours. The solvent was removed in vacuo and the residual solid dissolved in water and made acidic with acetic acid. The solid was collected, washed with water and dried to give the title compound (32 g), m.p. = 305-308°.

(ii) 2-Methylthio-5,6,7,8-tetrahydroquinazolin-4-one.

2-Thioxo-5,6,7,8-tetrahydroquinazolin-4-one (18.2 g, 0.1 mol) was added to a solution of sodium hydroxide (4.4 g, 0.11 mol) in water (25 ml). Ethanol (100 ml) was introduced followed by methyl iodide (15.6 g, 0.11 mol) and the final solution stirred at 60° for two hours. The suspension was cooled and filtered and the solid washed with diethyl ether to give the title compound (17.6 g), m.p. = 215-219°.

(iii) 2-[(2-Methylphenyl)amino]-5,6,7,8-tetrahydroquinazolin-4-one

2-Methylthio-5,6,7,8-tetrahydroquinazolin-4-one (16.8 g, 0.085 mol) and o-toluidine (50 ml) were heated at 220° for 24 hours and allowed to cool. The effluent gases from this reaction were passed through a CHLOROS trap. The mixture was treated with 40-60 petroleum spirits and filtered and the solid collected and recrystallised from dimethyl sulphoxide/water to give the title compound (16.6 g), m.p. = 253-257°.

(iv) 4-Chloro-2-[(2-methylphenyl)amino]-5,6,7,8-tetrahydroquinazoline.

2-[(2-Methylphenyl)amino]-5,6,7,8-tetrahydroquinazolin-4-one (16 g, 0.063 mol) and redistilled phosphorous oxychloride (50 ml) were heated to reflux temperature for three hours, allowed to cool and evaporated to dryness. The residual oil was treated with ice-water and extracted with chloroform. The combined organic extracts were washed with sodium

bicarbonate solution, water, dried and filtered. The residue after evaporation was chromatographed on silica gel using chloroform as eluent, the appropriate fractions combined and evaporated to give a solid which was triturated with 60-80 petroleum spirits to give the title compound (6.1 g), m.p. = 116-124°.

(v) 2-[(2-Methylphenyl)amino]-4-(N-methylphenyl)amino-5,6,7,8-tetrahydroquinazoline hydrochloride.

4-Chloro-2-[(2-methylphenyl)amino]-5,6,7,8-tetrahydroquinazoline (2.73 g, 0.01 mol) and N-methyl aniline (1.07 g, 0.01 mol) were heated to reflux temperature in dioxane (50 ml) for sixteen hours and allowed to cool. The solvent was removed in vacuo and the residue dissolved in petroleum spirits and filtered. The solid was recrystallised from ethanol/diethyl ether, filtered and the solid washed with ether to give the title compound (0.98 g), m.p. = 222-226°.

$C_{22}H_{24}N_4$ .HCl .0.7H_2O .0.1EtOH

Found: C 66.70, H 6.50, N 13.86

Requires: C 67.14, H 6.59, N 14.10

Example 24

2-[(2-Methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride. !SK&F 99118!

Substituting N-methyl-o-toluidine (1.21 g, 0.01 mol) for N-methyl aniline and using corresponding molar proportions of other reagents as in Example 23 above gave a mixture which was heated to reflux temperature for sixteen hours and allowed to cool. The solvent was removed in vacuo and the residual oil dissolved in

chloroform, washed twice with sodium bicarbonate solution, water, dried and filtered. The oil obtained from evaporation of the solvent was chromatographed on silica gel using chloroform as eluent, the appropriate fractions combined and evaporated to give a pale orange oil. This was dissolved in ethanolic HCl and the solvent removed to give an oil which was triturated with diethyl/ether to give a solid. This was recrystallised from ethanol/diethyl ether, filtered and washed with ether to give the title compound (0.42 g) m.p. = 227-228°.

$C_{23}H_{26}N_4 .HCl .0.7H_2O$

Found: C 67.54, H 6.58, N 13.74, Cl^- 8.80

Requires: C 67.89, H 6.86, N 13.37, Cl^- 8.71

Example 25

2-[(2-Methylphenyl)amino)-4-(N-methylphenylamino)-cyclopenta[d]pyrimidine hydrochloride !SK&F 99149!

(i) 2-Methylthiocyclopenta[d]pyrimidin-4-one

Ethyl-2-oxocyclopentanecarboxylate (62.4 g, 0.4 mol) and S-methylthiouronium sulphate (111.2 g, 0.4 mol) were added to a solution of potassium hydroxide (36 g, 0.64 mol) in methanol (500 ml) and stirred at room temperature for two hours. This was poured into water (3000 ml) and extracted with chloroform. The combined extracts were dried, filtered and the solvent evaporated to give a solid which was triturated with diethyl ether and filtered to give the title compound (11.2 g) m.p. = 210-213°.

(ii) 2-[(2-Methylphenyl)amino]cyclopenta[d]pyrimidin-4-one.

2-Methylthiocyclopenta[d]pyrimidin-4-one (5.1 g, 0.028 mol) and o-toluidine 920 ml) were heated to 220° for sixteen hours and allowed to cool to give an oil. The effluent gases from this reaction were passed through a CHLOROS trap. This was triturated with 40-60 petroleum spirits and a solid filtered off and washed with more solvent to give the title compound (6.8 g), m.p. = 208-213°.

(iii) 4-Chloro-2-[(2-methylphenyl)amino]cyclopenta[d]-pyrimidine.

2-[(2-Methylphenyl)amino]cyclopenta[d]pyrimidin-4-one (6.7 g, 0.028 mol) and phosphorus oxychloride (70 ml) were heated together under reflux for three hours and then evaporated to dryness. The residual oil was added carefully to ice/ammonia solution and extracted with chloroform. The combined extracts were washed with sodium bicarbonate solution, water, filtered and dried to give an oil. This was chromatographed on silica gel using chloroform as eluent and the appropriate fractions were combined, evaporated and the residue triturated with 40-60 petroleum spirits to give the title compound (2.1 g), m.p. 135-142°.

(iv) 2-[(2-Methylphenyl)amino)]-4-(N-methylphenyl)amino-cyclopenta[d]pyrimidine hydrochloride.

4-Chloro-2-[(2-methylphenyl)amino]cyclopenta[d]-pyrimidine (1.0 g, 0.0038 mol) and N-methyl aniline (0.49 g, 0.0046 mol) were refluxed in dry dioxane (60 ml)

for sixteen hours. The mixture was evaporated to dryness and the resultant solid recrystallised from ethanol/diethyl ether, filtered and washed with ether to give the title compound (0.72 g), m.p = 210-218° (dec).

$C_{21}H_{22}N_4 .HCl .H_2O$

Found: C 65.28, H 6.25, N 14.33

Requires: C 65.53, H 6.55, N 14.55

Example 26

2-[(2-Methylphenyl)amino)-4-(N-methyl-2-methylphenyl-amino)cyclopenta[d]pyrimidine hydrochloride. !SK&F 99148!

4-Chloro-2-[(2-methylphenyl)amino]cyclopenta[d]-pyrimidine (1.0 g, 0.0038 mol) and N-methyl-o-toluidine (0.59 g, 0.0046 mol) were refluxed in dry dioxane (60 ml) for sixteen hours. The mixture was evaporated to dryness and the resultant solid triturated with diethyl ether to give a solid which was recrystallised from ethanol/diethyl ether, filtered and washed with diethyl ether to give the title compound (0.58 g), m.p. = 210-214°.

$C_{22}H_{24}N_4 .HCl .0.8H_2O$

Found: C 66.55, H 6.42, N 14.22

Requires: C 66.83, H 6.78, N 14.17

Example 27

2-Amino-4-(2-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine

(i) Ethyl 2-methyl-3-oxo-4-methoxybutyrate

Zinc (36.12 g, 0.55 mol), methoxyacetonitrile (26.18 g, 0.37 mol), benzene (370 ml) and a small amount of mercuric chloride were heated to reflux under nitrogen. A solution of ethyl 2-bromopropionate (100 g, 0.55 mol) in benzene was added dropwise over 2.5 h, then reflux continued for a further hour before cooling to room temperature. 10% Aqueous sulphuric acid (650 ml) was added, and the layers separated. The aqueous was further extracted with ether (2 x 250 ml), and the combined organic layers washed with water and aqueous $NaHCO_3$, then dried and evaporated. Distillation gave the title compound as an oil (36.53 g), b.p. 111°/12mm.

(ii) 2-Amino-5-methyl-6-methoxymethylpyrimidine-4-one

Guanidinium carbonate (8.8 g, 49 mmol) and ethyl 2-methyl-3-oxo-4-methoxybutyrate (17.0 g, 98 mmol) in ethanol (200 ml) were heated under reflux for 4.5 hours. The solvent was evaporated and the residue treated with ice-cold water (100 ml) and acidified to pH 5 with glacial acetic acid. The solid which precipitated was filtered off, washed with a small amount of cold water and dried to give the title compound (14.47 g), m.p. 237-239°C.

(iii) 2-Amino-4-chloro-5-methyl-6-methoxymethylpyrimidine

2-Amino-5-methyl-6-methoxymethylpyrimidine-4-one (7.0 g, 41 mmol) and phosphoryl chloride (21 ml) were heated at reflux for 70 min. Excess phosphoryl chloride

was evaporated off and the residue treated with ice (100 ml), then brought to pH 8 with ammonium hydroxide. The yellow solid was filtered off, and the filtrate reduced in volume to obtain further crops. The combined solids were washed with cold water and dried to give the title compound (5.75 g), m.p. 201-203°C.

(iv) 2-Amino-4-(2-methylphenylamino)-5-methyl-6-methoxymethylpyrimidine

2-Amino-4-chloro-5-methyl-6-methoxymethylpyrimidine (5.65 g, 30 mmol) and o-toluidine (7.06 g, 66 mmol) in n-butanol (100 ml) were heated under reflux for 4.5 h. The solvent was evaporated, the residue triturated with ether, and the solid filtered off and dissolved in a small volume of water. The solution was raised to pH 8 with ammonium hydroxide and extracted repeatedly with chloroform. The combined extracts were dried and evaporated, and the residue crystallised from chloroform/ether to give the title compound (1.18 g), m.p. 148-149°C.

$C_{14}H_{18}N_4O$ .0.25H_2O

Found C 64.24, H 6.90, N 21.23

Requires C 63.97, H 7.09, N 21.31

Example 28

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-aminopyrimidine hydrochloride

(i) 6-Amino-2-[(2-methylphenyl)amino]pyrimidin-4-one

6-Amino-2-(nitroamino)pyrimidin-4-one (4.28 g, 25 mmol) and o-toluidine (6.42 g, 60 mmol) were added to dry

pyridine (50 ml), and the mixture heated to reflux for 48 hours. The pyridine was evaporated in vacuo, and the oily residue boiled with ethyl acetate, then allowed to cool. The resulting solid was mainly unreacted starting material, and was filtered off and discarded (1.46 g). The filtrate was extracted with aqueous sodium hydroxide, and the extracts neutralised with hydrochloric acid and re-extracted with ethyl acetate. Drying and evaporation of the organic extracts, and trituration with ether gave the title compound (2.3 g, 42%), m.p. 142-147°C.

(ii) 4-Amino-6-chloro-2[(2-methylphenyl)amino]pyrimidine

6-Amino-2-[(2-methylphenyl)amino]pyrimidin-4-one (2.0 g, 9.26 mmol) and phosphoryl chloride (20 ml, excess) were heated to reflux for 1 hour, then the solution was cooled and poured onto ice. The dark oil was extracted into ethyl acetate, then the aqueous layer was neutralised with sodium hydroxide and re-extracted with ethyl acetate. The combined organic extracts were washed with aqueous sodium carbonate, water and brine, dried and evaporated to a brown tar (1.2 g), which was used immediately without further purification.

(iii) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-aminopyrimidine hydrochloride

A mixture of 6-amino-4-chloro-2-[(2-methylphenyl)-amino]pyrimidine (1.2 g, 5.1 mmol) and N-methylaniline (3.0 g, excess) was heated to 170°C for 4 hours, then allowed to cool. The tarry product was washed with 1:1 ether/pet. ether, then chromatographed (silica, 0-1% MeOH in CH_2Cl_2). Product fractions were evaporated and

converted to the hydrochloride, which crystallised from ethanol/ether (0.08g), m.p. 218-220°C. A second crop (0.18 g) was obtained from the mother liquors.

$C_{18}H_{19}N_5$

Found C 63.00, H 5.99, N 20.20

Requires C 63.24, H 5.90, N 20.49

Example 29

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-propyl-6-methylpyrimidine hydrochloride

(i) Ethyl 2-propyl-3-oxobutyrate

To a solution of ethyl acetoacetate (39.04 g, 0.3 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (45.67 g, 0.3 mol) in dry benzene (500 ml) was added a solution of 1-iodopropane (51.0 g, 0.3 mol) in dry benzene (200 ml). The mixture was stirred for 3h, then the solid which precipitated was filtered off, washed with water, dried and evaporated in vacuo. The resulting brown oil was distilled twice under reduced pressure to give the title compound as a clear oil, yield 18.06 g, b.p. 80°C/18 mm.

(ii) 6-Methyl-2-thioxo-2-oxo-5-propylpyrimidine

Sodium (4.14 g, 0.18 mol) was dissolved in ethanol (150 ml), and a solution of ethyl 2-propyl-3-oxobutyrate (15.46 g, 0.09 mol) in ethanol was added, followed by thiourea (6.48 g, 0.09 mol). The mixture was heated under reflux for 4h, then the solvent was evaporated. The residue was dissolved in water and acidified to pH 4

with glacial acetic acid. The white solid which precipitated was filtered off, washed with water and dried to give the title compound (8.97 g), m.p. 207-208°C.

(iii) 2-Methylthio-5-propyl-6-methylpyrimidin-4-one

To a solution of sodium hydroxide (2.2 g, 55 mmol) in water (75 ml) was added 6-methyl-2-thioxo-4-oxo-5-propylpyrimidine (9.46 g, 50 mmol), followed by iodomethane (7.81 g, 55 mmol). The mixture was heated under reflux for 3h, then stirred at room temp. for 16h. Excess iodomethane was evaporated off, and the solution acidified to pH 4 with glacial acetic acid. The white solid which precipitated was filtered off, washed with water and dried to give the title compound (9.88 g), m.p. 178°C.

(iv) 2-(2-Methylphenylamino)-5-propyl-6-methylpyrimidin-4-one

2-Methylthio-5-propyl-6-methylpyrimidin-4-one (9.76 g, 49.2 mmol) and 2-methylaniline (37 ml, 350 mmol) were heated with stirring at 170°C for 17h. Excess toluidine was distilled off in vacuo, and the residue boiled with ethanol to give a white solid, which was filtered off, washed and dried to give the title compound (9.35 g), m.p. 223°C.

(v) 2-(2-Methylphenylamino)-4-chloro-5-propyl-6-methylpyrimidine

2-(2-Methylphenylamino)-5-propyl-6-methylpyrimidin-4-one (4.0 g, 15.5 mmol) and phosphoryl chloride (12 ml, excess) were heated under reflux for 3h. Excess phosphoryl chloride was evaporated off, and the residue

treated with ice-water. The mixture was extracted with chloroform, washed with aqueous sodium bicarbonate, dried and evaporated to give the product as a yellow oil which crystallised on standing; yield 3.68 g, m.p. 94-96°C.

(vi) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-propyl-6-methylpyrimidine hydrochloride

A solution of 2-(2-methylphenylamino)-4-chloro-5-propyl-6-methylpyrimidine (1.8 g, 6.53 mmol) and N-methylaniline (0.84 g, 7.84 mmol) in dioxan (20 ml) was heated under reflux for 17h. The solvent was evaporated, then the residue was boiled with ethanol and filtered hot. On allowing to cool, the filtrate deposited a yellow solid, which was filtered off and recrystallised from ethanol; yield 0.73 g, m.p. 258°C.

$C_{22}H_{26}N_4$ .HCl

Found C 68.88, H 7.22, N 14.60

Requires C 69.00, H 7.11, N 14.63

Example 30

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-(2-benzyloxyethyl)-6-methylpyrimidine

(i) 6-Methyl-2-thioxo-4-oxo-5-(2-hydroxyethyl)pyrimidine

2-Acetylbutyrolactone (64 g, 0.5 mol) and thiourea (38 g, 0.5 mol) were added to a solution of sodium (23 g, 1.0 mol) in absolute ethanol (600 ml). The mixture was stirred under reflux for 4 hours, then allowed to stand overnight. The solvent was removed by evaporation, the

residual solid was dissolved in water (500 ml), and the solution acidified with acetic acid. The deposited solid was filtered off, washed with water and dried; yield 34.8 g (40%), m.p. 264-272°C.

(ii) 6-Methyl-2-methylthio-4-oxo-5-(2-hydroxyethyl)-pyrimidine

A suspension of 6-methyl-2-thioxo-4-oxo-5-(2-hydroxyethyl)pyrimidine (10.0 g, 0.053 mol) in absolute ethanol (100 ml) was added to a solution of sodium hydroxide (2.4 g, 0.104 mol) in water (50 ml). Methyl iodide (8.4 g, 0.059 mol) was added and the mixture was stirred under reflux for 4 hours, then allowed to cool. The deposited solid was filtered off, washed with water and dried; yield 6.0 g (60%), m.p. 186-190°C.

(iii) 6-Methyl-2-methylthio-4-oxo-5-(2-benzyloxy-ethyl)pyrimidine

6-Methyl-2-methylthio-4-oxo-5-(2-hydroxyethyl)-pyrimidine (32.2 g, 0.186 mol) was added in portions to a stirred suspension of pet. ether-washed 60% sodium hydride (17.5 g, 0.437 mol) in dry dimethylformamide (400 ml) at a temperature of 30-40°C. The mixture was stirred for 30 min at this temperature, then a solution of benzyl bromide (32.9 g, 0.192 mol) in dimethylformamide (50 ml) was added dropwise over 10 min to the stirred mixture. The mixture was stirred for 1 hour at room temperature, then poured into a solution of water (500 ml) containing ammonium chloride, and allowed to stand. The deposited solid was filtered off, dried, and recrystallized from ethyl acetate. The product was collected as a white solid; yield 29.5 g (57%), m.p.-139-144°C.

(iv) 6-Methyl-2-[(2-methylphenyl)amino]-4-oxo-5-(2-benzyloxyethyl)pyrimdine

A mixture of 6-methyl-2-methylthio-4-oxo-5-(2-benzyloxyethyl)pyrimidine (29 g, 0.104 mol) and o-toluidine (150 ml, excess) was stirred at 200°C for 16 hours, then allowed to stand overnight. The solidified residue was triturated with diethyl ether to obtain the title compound; yield 29.9 g (82%), m.p. 162-168°C.

(v) 6-Methyl-2-[(2-methylphenyl)amino]-4-chloro-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-[(2-methylphenyl)amino]-4-oxo-5-(2-benzyloxyethyl)pyrimidine (25 g, 0.071 mol) and phosphoryl chloride (150 ml, excess) was stirred under reflux for 1 hour, the excess phosphoryl chloride removed by evaporation, and the residual oil treated with an excess of ice/water. The crude product was extracted with chloroform, the organic layer washed with saturated sodium bicarbonate and water, dried over $MgSO_4$ and the solvent evaporated, the product being a pale yellow viscous oil; yield 14 g.

(vi) 6-Methyl-2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-[(2-methylphenylamino]-4-chloro-5-(2-benzyloxyethyl)pyrimidine (1.0 g, 2.72 mmol) and an excess of N-methylaniline (3 ml) was stirred and heated at 180-200°C for 2 hours. After cooling, the crude oil was purified by chromatography (silica gel, chloroform). A further 2 columns were required to obtain the product as a viscous oil; yield 200 mg.

$C_{28}H_{30}N_4O$ .0.2$CHCl_3$ .0.1H_2O

Calc: C 72.95, H 6.60, N 12.06

Found: C 73.05, H 6.62, N 12.03

Example 31

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-5-(2-benzyloxyethyl)-6-methylpyrimidine

(i) 6-Methyl-2-[(2-methylphenyl)amino]-4-[N-methyl-(2-methylphenyl)amino]-5-(2-benzyloxyethyl)pyrimidine

A mixture of 6-methyl-2-[(2-methylphenyl)amino]-4-chloro-5-(2-benzyloxyethyl)pyrimidine (2.0 g, 0.0544 mol) and N-methyl-o-toluidine (5 ml, excess) was stirred at 200°C for 2 hours. After cooling, the crude residue was purified by silica gel chromatography, eluted with $CHCl_3$. A second column was required to obtain the product as a pale orange-coloured oil; yield 0.2 g.

$C_{29}H_{32}N_4O$ .0.3$CHCl_3$ .0.1H_2O

Calc: C 71.79, H 6.68, N 11.43

Found: C 71.75, H 6.70, N 11.53

Example 32

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-(2-hydroxyethyl)-6-methylpyrimidine

6-Methyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino)-5-(2-benzyloxyethyl)pyrimidine (2.3 g, 5.25 mmol) was mixed with 10% palladium on carbon in absolute ethanol (100 ml) and hydrogenated at 50 psi and

50°C for 12 hours. The product obtained by evaporation of the filtrate was crystallized from ethanol/diethyl ether and finally purified by silica gel chromatography, eluted with $CHCl_3$/MeOH (25:1). The product was obtained as a pale grey solid; yield 0.4 g (22%), m.p. 98-100°C.

$C_{21}H_{24}N_4O$

Calc: C 72.39, H 6.94, N 16.08

Found: C 72.11, H 7.04, N 15.90

Example 33

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino(-5-(2-hydroxyethyl)-6-methylpyrimidine

A mixture of 6-methyl-2-[(2-methylphenylamino]-4-(N-methyl-2-methylphenylamino)-5-(2-benzyloxyethyl)pyrimidine (0.7 g, 1.55 mmol) and 10% palladium on carbon catalyst (0.35 g) in absolute ethanol (50 ml) was hydrogenated at 50 psi and 50°C for 6 hours, followed by further reduction for 4 hours with fresh catalyst. After separation of the catalyst the filtrate was chromatographed (silica gel, $CHCl_3$/MeOH (25:1)). Product fractions were evaporated and triturated with pet. ether to give the title compound as a white crystalline solid; yield 0.13 g (23%), m.p. 161-163°C.

$C_{22}H_{26}N_4O \cdot 0.3H_2O$

Calc: C 71.82, H 7.28, N 15.32

Found: C 71.57, H 7.11, N 14.93

Example 34

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(benzyloxymethyl)pyrimidine hydrochloride

(i) 2-Thioxo-6-(benzyloxymethyl)pyrimid-4-one

To a solution of sodium (5.26 g, 0.224 mol) in ethanol (250 ml) was added thiourea (8.69 g, 0.114 mol) and ethyl 4-benzyloxyacetoacetate (27.0 g, 0.114 mol) and the mixture heated under reflux for 3 hours. The solvent was evaporated off and water (300 ml) added, followed by glacial acetic acid to pH 4. The resulting solid was filtered, washed and dried to give the title compound (22.12 g), m.p. 182-185°C.

(ii) 2-Methylthio-6-(benzyloxymethyl)pyrimid-4-one

To a solution of sodium hydroxide (2.3 g, 0.0581 mol) in water (15 ml) was added 2-thioxo-6-(benzyloxymethyl)-pyrimid-4-one in ethanol (150 ml) and iodomethane (8.25 g, 0.0581 mol). The mixture was stirred at room temperature for 16 hours. The resulting solid was filtered off, washed and dried to yield the title compound (9.20 g), m.p. 156-158°C.

(iii) 2-(2-Methylphenylamino)-6-(benzyloxymethyl)-pyrimid-4-one

2-Methylthio-6-(benzyloxymethyl)pyrimid-4-one (13.0 g, 0.065 mol) and o-toluidine (20.856 g, 0.195 mol) were heated with stirring under nitrogen at 200°C for 16 hours. After cooling, the mixture was triturated with ether to give a brown solid which was filtered off, washed and dried (11.30 g) m.p. 95-98°C.

(iv) 2-(2-Methylphenylamino)-4-chloro-6-(benzyloxy-methyl)pyrimidine.

2-(2-Methylphenylamino)-6-(benzyloxy-methyl)pyrimid-4-one (3.14 g, 0.0098 mol) and phosphoryl chloride (30 ml, excess) were heated with stirring under reflux for 1 hour. The phosphoryl chloride was evaporated off and the residue poured onto iced water, neutralised and extracted with chloroform. The combined extracts were dried, filtered and evaporated to an oil. This was purified by flash chromatography (silica, dichloromethane / 40-60 petroleum ether) to give the title compound as a yellow oil (1.33 g).

(v) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(benzyloxymethyl)pyrimidine hydrochloride.

2-(2-Methylphenylamino)-4-chloro-6-(benzyloxymethyl)pyrimidine (1.33 g, 0.0039 mol) and N-methylaniline (0.5 g, 0.0047 mol) in 1,4-dioxane were stirred and heated under reflux for 16 hours. The solvent was evaporated off and the residue triturated with ether to give a white solid. This was filtered off, recrystallised from methanol/ether and dried to give the title compound (0.6 g), m.p. 180°C.

$C_{26}H_{26}N_4O$ .HCl .0.32H_2O .0.1C_2H_5OH.

Found: C 69.04, H 6.09, N 12.28

Requires: C 68.80, H 6.22, N 12.26

Example 35

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-methoxymethylpyrimidine hydrochloride

(i) 2-Methylthio-6-(methoxymethyl)pyrimid-4-one

To a solution of potassium hydroxide (92.1 g, 1.642 mol) in methanol (2500 ml) was added methyl 4-methoxyacetoacetate (150 g, 1.026 mol) and 2-methyl-2-thiopseudourea sulphate (285.6 g, 1.026 mol). The mixture was stirred at room temperature for 3 hours. The solvent was evaporated off and water (500 ml) added, followed by glacial acetic acid to pH 4. The resulting solid was filtered off, washed and dried to yield the title compound (166.02 g), m.p. 184-186°C.

(ii) 2-(2-Methylphenylamino)-6-(methoxymethyl)pyrimid-4-one

2-Methylthio-6-methoxymethylpyrimid-4-one (80 g, 0.43 mol) and o-toluidine (138.55 g, 1.29 mol) were heated to 200°C under nitrogen with stirring for 16 hours. On cooling the product crystallised out and was filtered off, washed with ether and dried to yield the title compound (86.12 g), m.p. 140-145°C.

(iii) 2-(2-Methylphenylamino)-4-chloro-6-(methoxymethyl)pyrimidine.

2-(2-Methylphenylamino)-6-methoxymethylpyrimid-4-one (86.0 g, 0.351 mol) and phosphoryl chloride (500 ml, excess) were heated with stirring under reflux for 1 hour. The excess phosphoryl chloride was evaporated off and the residue poured onto iced water, neutralised and extracted using chloroform (x3). The combined extracts were dried, filtered and evaporated to an oil. This was purified by flash chromatography (silica, dichloromethane / 40-60 petroleum ether) to give the title compound as a yellow oil (66.0 g).

(iv) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(methoxymethyl)pyrimidine hydrochloride.

2-(2-Methylphenylamino)-4-chloro-6-(methoxymethyl)pyrimidine (37.0 g, 0.141 mol) and N-methylaniline (18.10 g, 0.169 mol) in 1,4-dioxane were stirred and heated under reflux for 16 hours. On cooling, the product crystallised out and was filtered off, washed and recrystallised from ethanol to give the title compound (19.36 g), m.p. 205-207°C.

$C_{20}H_{22}N_4O$ .HCl .0.21C_2H_5OH

Found: C 64.27, H 6.39, N 14.58

Requires: C 64.77, H 6.25, N 15.11

Example 36

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-hydroxymethylpyrimidine

To a solution of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(methoxymethyl)pyrimidine hydrochloride (5.0 g, 0.0135 mol) in dichloromethane (25 ml) was added dropwise boron tribromide (16.93 g, 0.0676 mol) in dichloromethane (5 ml), keeping the temperature between -10 & 0°C. After a further hour at 0°C, the solution was poured on to iced water and basified to pH 14 using sodium hydroxide. The mixture was extracted using dichloromethane (x3), and the combined extracts dried, filtered and evaporated. The residue was purified using flash chromatography (silica, methanol/dichloromethane), triturated with ether and the resulting crystals filtered and dried to yield the title compound (3.94 g), m.p. 134-136°C.

$C_{19}H_{20}N_4O$ .0.02$C_4H_{10}O$ .0.07H_2O

Found: C 70.75, H 6.34, N 17.14

Requires: C 71.23, H 6.29, N 17.49

Example 37

2-(2-Methylphenylamino)-4-(N-methylphenylamino)pyrimidine-6-carboxaldehyde

To a stirring solution of oxalyl chloride (2.094 g, 0.0165 mol) in dichloromethane (50 ml) at -50°C was added dimethylsulphoxide (2.808 g, 0.036 mol) in dichloromethane (10 ml) dropwise, keeping the temperature below -50°C. After 10 mins, a solution of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(hydroxymethyl)pyrimidine (5 g, 0.015 mol) in dichloromethane (50 ml) was added dropwise over 15 mins and stirred for a further 30 mins. Triethylamine (3.821 g, 0.375 mol) was then added and the mixture allowed to warm to room temperature. Water (100 ml) was added and the mixture extracted with dichloromethane (x2). The organic extracts were combined, dried, filtered and evaporated. The residue was purified by flash chromatography (silica, dichloromethane/methanol) then recrystallised from acetone-water to yield the title compound (2.1 g), m.p. 115-117°C.

$C_{19}H_{18}N_4O$

Found: C 71.57, H 5.58, N 17.65

Requires: C 71.68, H 5.70, N 17.60

Example 38

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(methylthiomethyl)pyrimidine

(i) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(bromomethyl)pyrimidine

To a stirred solution of 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(hydroxymethyl)pyrimidine (5 g, 0.015 mol) in ether (100 ml) was added carbon tetrabromide (9.95 g, 0.03 mol) and triphenylphosphine (7.87 g, 0.03 mol). After 48 hours the ether was evaporated off and the residue purified by flash chromatography (silica, dichloromethane) to give an oil. This was triturated with 40-60 petroleum ether and the resulting solid filtered off, washed and dried (4.20 g).

(ii) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6-(methylthiomethyl)pyrimidine

Sodium thiomethoxide (1.097 g, 0.0157 mol) and 2-(2-methylphenylamino)-4-(N-methylphenylamino)-6-(bromomethyl)pyrimidine (3.0 g, 0.0078 mol) in methanol (150 ml) were stirred at room temperature for 16 hours. The solvent was evaporated off and the residue treated with water, then extracted with dichloromethane (x2). The organic extracts were combined, dried, filtered and evaporated, and the residue crystallised from acetonitrile to yield the title compound (2.23 g), m.p. 137-140°C.

$C_{20}H_{22}N_4S$

Found: C 68.69, H 6.32, N 16.08

Requires: C 68.54, H 6.33, N 15.99

Example 39

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine hydrochloride

(i) Ethyl-2-methyl-4-methoxyacetoacetate

To a stirring mixture of zinc (90.25 g, 1.38 mol) and mercuric chloride (trace) in dry benzene (1000 ml) under nitrogen was added methoxyacetonitrile (65.32 g, 0.92 mol). The reaction was heated to reflux for 15 minutes, then ethyl bromoproprionate in dry benzene (500 ml) added dropwise over 2.5 hours and refluxed for a further hour. After cooling, 10% sulphuric acid (1800 ml) was added and the mixture extracted with ether (x3). The extracts were washed with dilute sodium bicarbonate, dried, filtered and evaporated to an oil. Distillation under reduced pressure gave the title compound (91.2 g), b.p. 100-116°C/9mm.

(ii) 2-Methylthio-5-methyl-6-(methoxymethyl)pyrimid-4-one

To a solution of potassium hydroxide (44.88 g, 0.8 mol) in methanol (1.2 l) was added ethyl-2-methyl-4-methoxyacetoacetate (87.1 g, 0.5 mol) and 2-methyl-2-thiopseudourea sulphate (139.2 g, 0.5 mol). The mixture was stirred at room temperature for 3 hours, the solvent evaporated off, and water (350 ml) added, followed by glacial acetic acid to pH 4. The resulting solid was filtered off, washed and dried to yield the title compound (78.00 g), m.p. 184-186°C.

(iii) 2-(2-Methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimid-4-one

2-methylthio-5-methyl-6-(methoxymethyl)pyrimid-4-one (78 g, 0.39 mol) and o-toluidine (167.00 g, 1.56 mol) were heated to 200°C under nitrogen with stirring for 16 hours. On trituration with ether the product crystallised out and was filtered off, washed and dried (88 g), m.p. 174-176°C.

(iv) 2-(2-Methylphenylamino)-4-chloro-5-methyl-6-(methoxymethyl)pyrimidine.

2-(2-Methylphenylamino)-5-methyl-6-(methoxymethyl)-pyrimid-4-one (68.0 g, 0.26 mol) and phosphoryl chloride (500 ml, excess) were heated with stirring under reflux for 1 hour. The excess phosphoryl chloride was evaporated off and the residue poured onto iced water, neutralised with sodium bicarbonate and extracted using chloroform (x3). The combined extracts were dried, filtered and evaporated to yield the title compound as an oil (70.82 g).

(v) 2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine hydrochloride.

2-(2-Methylphenylamino)-4-chloro-5-methyl-6-(methoxymethyl)pyrimidine (9.0 g, 0.032 mol) and N-methylaniline (4.109 g, 0.038 mol) in 1,4-dioxane (350 ml) were stirred and heated under reflux for 16 hours. On cooling the product crystallised out, and was filtered off, washed and recrystallised from acetone-ether to give the title compound (12.32 g), m.p. 167-168°C.

$C_{21}H_{24}N_4O$ .HCl

Found: C 65.73, H 6.57, N 14.43

Requires: C 65.53, H 6.55, N 14.56

Example 40

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(hydroxymethyl)pyrimidine

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5-methyl-6-(methoxymethyl)pyrimidine hydrochloride (5.6 g, 0.0137 mol) in dichloromethane (25 ml) was cooled to -10°C and boron tribromide (17.18 g, 0.685 mol) in dichloromethane (10 ml) added dropwise, keeping the temperature between -10 & 0°C. After a further 30 minutes at 0°C the solution was poured on to iced water, basified to pH 14 using sodium hydroxide and extracted using dichloromethane (x3). The organic extracts were combined, dried, filtered and evaporated. The residue was recrystallised from ethanol and the resulting crystals filtered off, washed and dried to yield the title compound (4.58 g), m.p. 129-130°C.

$C_{20}H_{22}N_4O$

Found: C 71.54, H 6.67, N 16.48

Requires: C 71.83, H 6.63, N 17.75

Example 41

2-(2-Phenylamino)-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride

(i) 2-Methylthio-4-oxo-5,6,7,8-tetrahydroquinazoline

Ethyl 2-oxocyclohexanecarboxylate (53 g, 0.312 mol) and S-methyl thiouronium sulphate (82 g, 0.312 mol) were added to a solution of potassium hydroxide (28 g, 0.5 mol) in methanol (500 ml). The mixture was stirred at room

temperature for 16h, poured into water (1.5 l), acidified with glacial acetic acid, and stirred for 30 min before filtering off the product, washing with water and drying; yield 36 g (55%), m.p. 233-240°C.

(ii) 2-(Phenylamino)-4-oxo-5,6,7,8-tetrahydroquinazoline

A mixture of 2-methylthio-4-oxo-5,6,7,8-tetrahydroquinazoline (20 g, 0.102 mol) and aniline (50 ml, excess) was heated at 200°C for 16h, then allowed to cool. The solid mass was triturated with ether, and the solid product filtered off, washed with ether and dried; yield 21 g (85%), m.p. 267-270°C.

(iii) 4-Chloro-2-(2-phenylamino)-5,6,7,8-tetrahydroquinazoline

2-Phenylamino-4-oxo-5,6,7,8-tetrahydroquinazoline (10 g, 41.4 mmol) and phosphoryl chloride (100 ml, excess) were heated under reflux for 3 hours, then evaporated to dryness. The oil was added carefully to ice/ammonia, and extracted with chloroform. The extracts were washed with sodium bicarbonate solution and water, dried and evaporated to give an oil, which was triturated with ether to obtain the title compound; yield 7.1 g (67%), m.p. 123-125°C.

(iv) 2-(2-Phenylamino)-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride

4-Chloro-2-(2-phenylamino)-5,6,7,8-tetrahydroquinazoline (2.0 g, 77 mmol) and N-methylaniline (5 ml, excess) were heated to 200°C for 3 hours. Chromatography (silica, chloroform), conversion to the hydrocchloride and crystallisation from ethanol/ether gave the title compound (0.48 g, 19%), m.p. 242-245°C.

$C_{21}H_{22}N_4$ .HCl

Found C 68.49, H 6.44, N 15.22, Cl 9.63

Requires C 68.74, H 6.32, N 15.27, Cl 9.66

Example 42

2-(2-Phenylamino)-4-(N-methyl2-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride

A mixture of 4-chloro-2-(phenylamino)-5,6,7,8-tetrahydroquinazoline (4.0 g, 15.4 mmol) and N-methyl-2-methylaniline (10 ml, excess) was heated to 200°C for 2 hours. Chromatography (silica, chloroform), conversion to the hydrochloride and crystallisation from ethanol/ether gave the title compound (0.28 g), m.p. 240-255°C.

$C_{22}H_{24}N_4$ .1.13HCl

Found C 68.36, H 6.57, N 14.32, Cl 10.08

Requires C 68.51, H 6.51, N 14.53, Cl 10.39

Example 43

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-thiopyrano[3,2-d]pyrimidine hydrochloride

(i) 7,8-Dihydro-4-hydroxy-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine

7,8-Dihydro-4-hydroxy-2-methylthio-6H-thiopyrano[3,2-d]pyrimidine (5 g, 0.023 mol) and 2-methylphenylamine (10 g) were heated at 200°C for 20h. After allowing to cool, the reaction mixture was diluted with methanol, and

the resulting solid was collected by filtration, washed with methanol and dried; yield 4.8 g, m.p. 220-224°C.

(ii) 7,8-Dihydro-4-chloro-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine

7,8-Dihydro-4-hydroxy-2-methylthio-6H-thiopyrano[3,2-d]pyrimidine (4 g, 0.014 mol) and phosphorus oxychloride (40 ml) were heated under reflux for 1h. The excess phosphorus oxychloride was evaporated under reduced pressure. The residue was treated with ice/water, basified with conc. ammonia solution and extracted with chloroform (3x150 ml). The chloroform extracts were combined, dried over magnesium sulphate, filtered and evaporated under reduced pressure to give the title compound as an oil; yield 4.2 g.

(iii) 7,8-Dihydro-4-(N-methylphenylamino)-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine hydrochloride.

7,8-Dihydro-4-chloro-2-(2-methylphenylamino)-6H-thiopyrano[3,2-d]pyrimidine (3 g, 0.01 mol) and N-methylaniline (2.2 g, 0.02 mol) were heated at 150°C for 1h. After allowing to cool down the reaction mixture was diluted with diethyl ether, and the resulting solid was collected by filtration, washed with ether and dried. The solid was recrystallized from ethanolic HCl, then ethanol, to give the title compound; yield 1.4 g, m.p. 224-226°C.

$C_{21}H_{22}N_4S$ .HCl

Found C 62.93, H 5.79, N 13.74, S 7.81, Cl 8.81

Requires C 63.22, H 5.81, N 14.04, S 8.04, Cl 8.89

Example 44

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-5,7-dihydrothieno[3,4-d]pyrimidine hydrochloride

(i) 2-(2-Methylthio)-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine

Methyl-3-oxotetrahydrothiophene-4-carboxylate (32.0 g, 0.2 mol) and S-methylisothiouranium sulphate (55.6 g, 0.2 mol) were added to a solution of potassium hydroxide (17.9 g, 0.32 mol) in methanol (300 ml). The mixture was stirred at room temperature for 16 hours, then poured into water (approx. 3 l). The mixture was acidified with acetic acid, the white solid filtered off, washed with water and dried; yield 34.2 g (85%), m.p. 270-273°C.

(ii) 2-[(2-Methylphenyl)amino]-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine

2-(2-Methylthio)-4-oxo-5,7-dihydrothieno[3,4-d]pyrimidine (32 g, 0.16 mol) was mixed with o-toluidine (100 ml, excess) and the mixture stirred and heated at 200°C for 6 hours, then allowed to cool. The solid mass was was triturated with diethyl ether, and the grey coloured solid filtered off, washed with ether and dried; yield 30 g (73%), m.p. 247-251°C.

(iii) 2-[(2-Methylphenyl)amino]-4-chloro-5,7-dihydrothieno[3,4-d]pyrimidine

2-[(2-Methylphenyl)amino]-4-oxo-5,7-dihydrothieno-[3,4-d]pyrimidine (30 g, 0.115 mol) was mixed with phosphoryl chloride (150 ml, excess) and the mixture was

stirred under reflux for 2 hours, then evaporated to dryness. The residual oil was treated with ice-water, extracted with 3 x 100 ml $CHCl_3$, the extracts washed with sat. $NaHCO_3$ and water, dried over $MgSO_4$, and the solvent evaporated. The dark oil was purified by silica gel chromatography and eluted with $CHCl_3$; yield 6.0 g (18%).

(iv) 2-[(2-Methylphenyl)amino]-4-(N-methyl-2-methylphenyl)amino-5,7-dihydrothieno[3,4-d]pyrimidine

2-[(2-Methylphenyl)amino]-4-chloro-5,7-dihydrothieno[3,4-d]pyrimidine (2.0 g, 7.22 mmol) was mixed with N-methyl aniline (0.91 g, 8.59 mmol) in 1,4-dioxane (80 ml). The mixture was stirred under reflux for 16 hours, then evaporated to dryness. The residual solid was triturated with diethyl ether then recrystallized from aqueous ethanol; yield 1.4 g (58%), m.p. 195-198°C.

$C_{20}H_{20}N_4S$ .0.7HCl .0.6H_2O

Calc: C 62.43, H 5.73, N 14.56, Cl 6.45

Found: C 62.57, H 5.53, N 14.71, Cl 6.64

Example 45

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-5,7-dihydrothieno[3,4-d]pyrimidine

2-[2-(2-methylphenyl)amino]-4-chloro-5,7-dihydrothieno[3,4-d]pyrimidine (5.0 g, 0.018 mol) was mixed with N-methyl-o-toluidine (2.79 g, 0.0216 mol) and fused at 160°C for 2 hours. After cooling, the oil was triturated with diethyl ether and the resulting solid filtered off and chromatographed (silica gel, $CHCl_3$); yield 2.76 g (42%), m.p. 162-165°C.

$C_{21}H_{22}N_4S$

Calc: C 69.58, H 6.11, N 15.46, S 8.85

Found: C 69.52, H 6.09, N 15.35, S 9.05

Example 46

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-6-oxo-5,7-dihydrothieno[3,4-d]pyrimidine

A solution of m-chloroperbenzoic acid (0.61 g, 3.58 mmol) in dry dichloromethane (20 ml) was added dropwise to a stirred solution of 2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl)amino-5,7-dihydrothieno[3,4-d]pyrimidine (1.0 g, 2.76 mmol) in dry dichloromethane (25 ml) at -35° to -40°C. The mixture was stirred for 1 hour at this temperature then allowed to stand overnight. Ammonia gas was bubbled through the solution for 5 min, then the deposited solid was filtered off, washed with dichloromethane and discarded. The combined filtrate was evaporated to dryness and the residual oil was purified by silica gel chromatography, eluted with $CHCl_3$. The product was obtained as an orange coloured solid; yield 0.38 g (38%), m.p. 100-105°C.

$C_{21}H_{22}N_4OS \cdot 0.4H_2O \cdot 0.1C_2H_5OH$

Calc: C 65.23, H 6.04, N 14.35, S 8.22

Found: C 64.90, H 5.85, N 14.39, S 8.41

Example 47

2-[(2-Methylphenylamino-4-(N-methyl-2-methylphenylamino)-6,6-dioxo-5,7-dihydrothieno[3,4-d]pyrimidine

A solution of m-chloroperbenzoic acid (3.56 g, 0.0207 mol) in dry dichloromethane (20 ml) was added dropwise with stirring to a solution of 2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl)amino-5,7-dihydrothieno[3,4-d]pyrimidine (2.5 g, 0.0069 mol) in dry dichloromethane (50 ml) at 25-30°C. The mixture was stirred at room temperature for 16 hours, ammonia gas bubbled through the solution for 10 min, and the deposited solid filtered off and discarded. The filtrate was columned on silica gel, eluted with chloroform. A second column was required to obtain the product as a pale brown solid, m.p. 177-179°C.

$C_{21}H_{22}N_4O_2S$

Calc: C 63.94, H 5.62, N 14.20

Found: C 63.68, H 5.58, N 13.91

Example 48

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-6,7-dihydrothieno[3,2-d]pyrimidine

(i) 2-Thio-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine

2-Carbomethoxy-3-oxotetrahydrothiophene (55 g, 0.316 mol) was added to a solution of sodium (14.5 g, 0.632 mol) in ethanol (500 ml), followed by the addition of thiourea (24 g, 0.316 mol). The mixture was stirred for 24 hours at room temperature, then the solvent evaporated. The residual solid was dissolved in water, acidified with glacial acetic acid and the deposited solid filtered off, washed with water, and dried; yield 25 g (42%).

(ii) 2-Methylthio-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine

2-Thio-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine (25 g, 0.134 mol) was added to a solution of sodium hydroxide (5.88 g, 0.147 mol) in water (50 ml) and ethanol (500 ml). Methyl iodide (20.8 g, 0.147 mol) was added, and the mixture was stirred under reflux for 16 hours. After cooling, the solid was filtered off, washed with diethyl ether and dried; yield 19.5 g (69%), m.p. 265-270°C.

(iii) 2-[(2-Methylphenyl)amino]-4-oxo-6,7-dihydrothieno[3,2-d]pyrimidine

A mixture of 2-methylthio-4-oxo-6,7-dihydrothieno-[3,2-d]pyrimidine (19.5 g, 0.0975 mol) and o-toluidine (80 ml, excess) was stirred and heated at 180-200°C for 16 hours. After cooling, the mixture was poured into diethyl ether (600 ml) and stirred for 30 min at room temperature, then the solid was filtered off, washed with ether and dried; yield 16.1 g (64%), m.p. 249-252°C.

(iv) 2-[(2-Methylphenyl)amino]-4-chloro-6,7-dihydrothieno[3,2-d]pyrimidine

2-[(2-Methylphenyl)amino]-4-oxo-6,7-dihydrothieno-[3,2-d]pyrimidine (11.0 g, 0.0424 mol) was mixed with phosphoryl chloride (150 ml, excess) and stirred under reflux for 90 min. The excess acid chloride was removed by evaporation, the residual oil treated with ice/water and extracted with $CHCl_3$, then the extracts were washed with sat. $NaHCO_3$ and water, dried over $MgSO_4$ and the solvent evaporated leaving an oil; yield 12.3 g (greater than theoretical), used without further purification.

(v) 2-[(2-Methylphenyl)amino)-4-(N-methylphenyl)amino]-6,7-dihydrothieno[3,2-d]pyrimidine

2-[(2-Methylphenyl)amino]-4-chloro-6,7-dihydrothieno[3,2-d]pyrimidine (2.5 g, 9 mmol, crude) was mixed with N-methylaniline (9 ml, excess) and the mixture was stirred at 200°C for 2 hours. After cooling, the product was purified by silica gel chromatography, eluted with EtOAc/pet. ether (1:4). The title compound was obtained as a pale brown solid; yield 1.1 g (34%), m.p. 184-185°C.

$C_{20}H_{20}N_4S$ .0.3H_2O

Calc: C 67.88, H 5.88, N 15.83, S 9.08
Found: C 67.71, H 5.77, N 15.70, S 9.06

Example 49

2-(2-Methylphenylamino)-4-(N-methyl-2-methylphenylamino)-6,7-dihydrothieno[3,2-d]pyrimidine

A mixture of 2-[(2-Methylphenyl)amino]-4-chloro-6,7-dihydrothieno[3,2-d]pyrimidine (4.9 g, 0.0176 mol) and N-methyl-o-toluidine (15 ml, excess) was stirred at 200°C for 3 hours. After cooling, the crude oil was dissolved in $CHCl_3$ and the oil purified by silica gel chromatography, eluted with $CHCl_3$. A further column was required to obtain the product as a grey coloured solid, m.p. 162-165°C.

$C_{21}H_{22}N_4S$

Calc: C 69.58, H 6.12, N 15.46
Found: C 69.63, H 6.07, N 15.31

Example 50

2-(2-Methylphenylamino)-4-(N-methylphenylamino)-thiopyrano[4,3-d]pyrimidine hydrochloride

(i) 2-(Methylthio)thiopyrano[4,3-d]pyrimidin-4-one

To a solution of potassium hydroxide (1.08 g, 19 mmol) in methanol (25 ml) was added 3-carbomethoxytetrahydro-1,4-thiapyrone (2.0 g, 12 mmol) and S-methylisothiouronium sulphate (3.34 g, 12 mmol). After stirring at room temperature for 2 hours, the solution was evaporated to low volume, poured into water (150 ml) and acidified to pH 4 with glacial acetic acid. The white solid which precipitated was filtered off, washed with water and dried to give the title compound (0.81 g), m.p. 212°C.

(ii) 2-[(2-Methylphenyl)amino]thiopyrano[4,3-d]pyrimidin-4-one

A mixture of 2-(methylthio)thiopyrano[4,3-d]pyrimidin-4-one (18.0 g, 84 mmol) and o-toluidine (63 g, excess) was heated at 160°C for 17 hours. Excess toluidine was distilled off under reduced pressure, and the residue boiled with ethanol to give a yellow solid. This was filtered off and washed with ether to give the title compound (15.6 g), m.p. 237-240°C.

(iii) 2-[(2-Methylphenyl)amino]-4-chlorothiopyrano-[4,3-d]pyrimidine

A mixture of 2-[(2-methylphenyl)amino]thiopyrano-[4,3-d]pyrimidin-4-one (13.46 g, 49 mmol) and phosphoryl chloride (40 ml, excess) was heated under reflux for 3 hours. The excess phophoryl chloride was evaporated under reduced pressure, and the residue treated with ice-cold water, then extracted 3x with chloroform. The combined extracts were washed with aqueous sodium bicarbonate, water and brine, dried and evaporated to a dark red oil.

Chromatography (silica, CH_2Cl_2/MeOH) gave the title compound as a yellow oil (4.33 g).

(iv) 2-[(2-Methylphenyl)amino]-4-(N-methylphenylamino)-thiopyrano[4,3-d]pyrimidine hydrochloride

A solution of 2-[(2-methylphenyl)amino]-4-chlorothiopyrano[4,3-d]pyrimidine (2.0 g, 6.9 mmol) and N-methylaniline (0.88 g, 8.2 mmol) in dioxan (60 ml) was heated under reflux for 16 hours. The solvent was evaporated, and the residue crystallised from ethanol to yield the title compound (0.92 g), m.p. 225°C.

$C_{21}H_{22}N_4S$ .HCl

Found C 63.26, H 5.82, N 14.18, Cl 8.73

Requires C 63.22, H 5.81, N 14.04, Cl 8.89

Example 51

2-(2-Methylphenylamino)-4-(N-methylphenylamino)6-oxothiopyrano[4,3-d]pyrimidine

A solution of 2-[(2-methylphenyl)amino]-4-(N-methylphenylamino)thiopyrano[4,3-d]pyrimidine hydrochloride (2.0 g, 5 mmol) in dichloromethane was washed with aqueous sodium bicarbonate then brine, dried over potassium carbonate, and the drying agent filtered off. The filtrate was cooled to -40°C, and a solution of m-chloroperbenzoic acid (1.12 g, 6.5 mmol) in dichloromethane added dropwise. After a further 0.75 h at -40°C, the cooling bath was removed and ammonia gas passed through the solution for 5 min. The precipitate was filtered off on celite, and the filtrate evaporated to an

orange oil, which crystallised on trituration with ether. Recrystallisation from chloroform/ethanol, then from methanol, gave the title compound (0.75 g), m.p. 186°C.

$C_{21}H_{22}N_4OS$ .0.9% w/w CH_3OH

Found C 66.05, H 5.88, N 14.69, S 8.75

Requires C 66.38, H 6.09, N 14.66, S 8.39

Biological Data.

(A) H^+K^+ATPase Activity.

The effects of a single high concentration (100 μM) of a compound of structure (I) on K-stimulated ATPase activity in lyophilised gastric vesicles was determined. Preferred compounds of structure (I) were also tested over a range of concentrations to determine IC_{50} values.

(i) Preparation of lyophilised gastric vesicles (H/K-ATPase).

Lyophilised gastric vesicles were prepared from pig fundic mucosa after the method of Keeling et. al. (Biochem. Pharmacol., 34, 2967, 1985).

(ii) K^+-stimulated ATPase activity.

K^+-stimulated ATPase activity was determined at 37° in the presence of the following : 10 mM Pipes/Tris buffer pH 7.0, 2 mM $MgSO_4$, 1 mM KCl, 2 mM Na_2ATP and 3-6 μg protein/ml lyophilised gastric vesicles. After incubation for 30 minutes, the inorganic phosphate hydrolysed from ATP was determined by the method of Yoda and Hokin (Biochem. Biophys. Res. Commun. 40, 880, 1970).

Compounds of structure (I) were dissolved in dimethylsulphoxide which up to the highest concentration used had no effect on K^+-stimulated ATPase activity.

The effect of the highest concentration of each compound of structure (I) on the recovery of a standard amount of inorganic phosphate was also determined.

(iii) Results.

The compounds of the examples had IC_{50} values of less than 50μM.

Example A

A tablet for oral administration is prepared by combining

	Mg/Tablet
Compound of structure (I)	100
lactose	153
Starch	33
crospovidone	12
microcrystalline cellulose	30
magnesium stearate	2
	330 mg

into a 9 mm tablet.

Example B

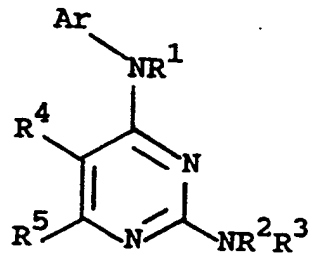
An injection for parenteral administration is prepared from the following

		%w:w
Compound of structure (I)		0,50% (w:v)
1M citric acid		30% (v:v)
sodium hydroxide (qs)		to pH 3.2
water for injection EP	to	100 ml

The compound of structure (I) is dissolved in the citric acid and the pH slowly adjusted to pH 3.2 with the sodium hydroxide solution. The solution was then made up to 100 ml with water, sterilised by filtration and sealed into appropriately sized ampoules and vials.

Claims.

1. A compound of structure (I)



(I)

in which

Ar is a phenyl ring which can be optionally substituted by one to three groups selected from hydroxy, halogen, CF_3, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylthio, cyano, amino, carbamoyl carboxy or C_{1-4}alkanoyl;

R^1 is hydrogen or C_{1-4}alkyl;

R^2 and R^3 are the same or different and are each hydrogen, C_{1-4}alkyl or Ar^1 where Ar^1 is as defined for Ar; or R^2 and R^3 together with the nitrogen atom to which they are attached form a saturated or unsaturated ring optionally containing one or more further heteroatoms.

one of R^4 and R^5 is hydrogen or C_{1-4}alkyl; and the other is hydrogen, C_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxyC_{1-4}alkyl, amino, C_{1-4}alkanoyl, C_{1-4}alkylthioC_{1-4}alkyl, $Ar^2(CH_2)_nOC_{1-4}$alkyl, in which Ar^2 is an optionally substituted phenyl ring as defined for Ar and n is 0 to 4; or $-(CH_2)_mAr^3$, in which m is 1 to 4 and Ar^3 is an optionally substituted phenyl ring as defined for Ar; or R^4 and

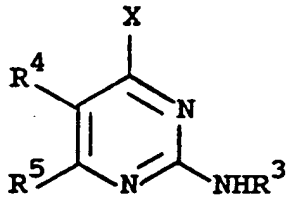
R^5 together with the carbon atoms to which they are attached form a 5- or 6-membered ring, optionally containing one or more heteroatoms;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 in which one of R^2 and R^3 is hydrogen and the other is an optionally substituted phenyl ring.

3. A compound according to claim 1 which is 5,6-dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenyl amino)pyrimidine hydrochloride, 5,6-dimethyl-2-[(2-methylphenyl)amino]-4-(N-methyl-phenylamino)pyrimidine hydrochloride, 5-methyl-6-n-propyl-2-[(2-methylphenyl)amino]-4-(N-methylphenylamino) pyrimidine hydrochloride, 2-[(2-methylphenyl)amino]-4-(N-methyl-2-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride, or 2-(2-phenylamino)-4-(N-methylphenylamino)-5,6,7,8-tetrahydroquinazoline hydrochloride.

4. A process for preparing a compound according to claim 1 which comprises reaction of a compound of structure (II)



(II)

in which R^3, R^4 and R^5 are as described for structure (I), and X is a group displaceable by an amine,

with an amine of structure $ArNR^1H$ in which Ar and R^1 are as described for structure (I), and optionally thereafter, forming a pharmaceutically acceptable salt.

5. A pharmaceutical composition comprising a compound of structure (I) or a pharmaceutically acceptable salt thereof as described in claim 1 in association with a pharmaceutically acceptable carrier.

6. A compound of structure (I) for use in therapy.

7. A compound of structure (II) as described in claim 4.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 91/01007

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 239/48 C 07 D 239/50 C 07 D 239/42
A 61 K 31/505 C 07 D 239/95 C 07 D 495/04 C 07 D 239/70

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 239/00 C 07 D 495/04

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	GB,A,1229413 (I.C.I.) 21 April 1971, see pages 1,2(I,1),7,16,17 ---	1,2,4,7
X	GB,A, 584917 (PARKE, DAVIS & CO.) 27 January 1947, see pages 1,6 (examples 7,8) ---	1
X	US,A,3478030 (J.H. SHORT) 11 November 1969, see columns 1-3 ---	1,4-7
X	US,A,2748124 (R.R. BURTNER) 29 May 1956, see columns 1-4 ---	1,4,7
X	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 21, July-August 1984, (US), H. GERSHON et al.: "Pyrimidines. 7. A Study of the chlorination of pyrimidines with phosphorus oxychloride in the presence of N,N-dimethylaniline", pages 1161-1167, see pages 1162-1166 --- -/-	1-7

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19-08-1991	18 OCT 1991
International Searching Authority	Signature of Authorized Officer
EUROPEAN PATENT OFFICE	MISS D. S. KOWALCZYK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, 1968, (Washington, US), G.J. ATWELL et al.: "Potential antitumor agents. VIII. Bisquaternary salts", pages 690-694, see pages 691-692 ---	1
X	CHEMICAL ABSTRACTS, vol. 71, 1969, page 295, abstract no. 30453h, (Columbus, Ohio, US), E.A. ARUTYUNYAN et al.: "Direct amination of uracils and related compounds", & IZV. AKAD. NAUK SSSR, SER. KHIM. 1969, (3), 655-62, see the abstract ---	1,2
X	CHEMICAL ABSTRACTS, vol. 93, 1980, pages 925-926, abstract no. 46582q, (Columbus, Ohio, US), A.V. IVASHCHENKO et al.: "Synthesis and study of derivatives of 2,4-diamino- and 2-amino-4-(1H-pyrazol-1-yl)pyrimidine", & KHIM. GETEROTSIKL. SOEDIN. 1980, (3), 404-7, see the abstract ---	1,2
X	CHEMICAL ABSTRACTS, vol. 95, 1981, page 648, abstract no. 97712f, (Columbus, Ohio, US), D. GHOSH: "2,4-Bis(arylamino)-6-methylpyrimidines as antimicrobial agents", & J. INDIAN CHEM. SOC. 1981, 58(5), 512-13, see the abstract ---	1,2,5,6
X	CHEMICAL ABSTRACTS, vol. 108, 1988, page 724, abstract no. 56043g, (Columbus, Ohio, US), K.M. GHONEIM et al.: "Synthesis and evaluation of some 2-, 4- and 2,4-di-substituted-6-methylpyrimidine derivatives for antimicrobial activity", & J. INDIAN CHEM. SOC. 1986, 63(10), 914-17, see the abstract ---	1,2,4,6
X	CHEMICAL ABSTRACTS, vol. 108, 1988, page 670, abstract no. 204585c, (Columbus, Ohio, US), K.M. GHONEIM et al.: "Synthesis and evaluation of some 2-, 4-, and 2,4-disubstituted-6-methylpyrimidine derivatives for antimicrobial activity", & EGYPT. J. PHARM. SCI. 1987, 28(1-4), 117-26, see the abstract ---	1-7
X	CHEMICAL ABSTRACTS, vol. 114, 1991, page 684, abstract no. 62037y, (Columbus, Ohio, US), K.M. GHONEIM et al.: "Synthesis of some Mannich bases of 2- and 4-amino- and 2,4-diamino-6-methylpyrimidines as potential biodynamic agents", & EGYPT. J. CHEM. 1987, (PUB. 1989), 30(6), 295-304, see the abstract --- -/-	1,5

III. DOCUMENTS CONSIDERED TO [redacted] ELEVANT (CONTINUED FROM THE SECOND [redacted] ET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	CHEMICAL ABSTRACTS, vol. 66, 1967, page 2735, abstract no. 28731a, (Columbus, Ohio, US), C.A.R. HURT et al.: "The synthesis of pyrimidoquinazolones", & TETRAHEDRON SUPPL. NO. 7, 227-32(1966), see the abstract	1
A	EP,A,0322133 (SMITHKLINE) 28 June 1989, see pages 1-4, claims	1,3-7
P,X	WO,A,9012790 (I.C.I.) 1 November 1990, see pages 24-44,51-76	1-3,7
P,X	EP,A,0404356 (SMITHKLINE) 27 December 1990, see the whole document	1,4-7

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. EP 9101007
SA 48029

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
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